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ERUPTIVE FEVER WITH INVOLVEMENT OF THE RESPIRATORY TRACT, CONJUNCTIVITIS, STOMATITIS AND BALANITIS

An Acute Clinical Entity, Probably of Infectious Origin; Report of Twenty Cases and Review of the Literature

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DURING the past several years, 20 cases of an unusual disease syndrome, which has had some mention in the literature of the past sixty years, have been observed at a military installation. The syndrome has been described under a variety of appellations such as eruptive fever with stomatitis and ophthalmia, erythema exudativum multiforme of Hebra, erythema or herpes iris conjunctivae, ectodermosis erosiva pluriorificialis and Stevens-Johnson syndrome. Such a terrifying array of unfamiliar and difficult names suggests, perhaps, why this disease remains an unknown and undiagnosed entity to most physicians. However, after one has seen a typical case the various clinical features fall into a rather easily recognized pattern which is difficult to mistake thereafter.

This condition is an acute, systemic, frequently febrile disease running a self-limited course of a few days to several weeks and involving, to varying degrees, the respiratory tract, skin and mucous membranes, chiefly those of the eyes, mouth and urethral meatus. The onset occurs usually with a cold, cough, malaise and sore throat, followed frequently by fever. After a few days an eruption appears in the mouth, characterized by clear vesicles, which usually rupture within twenty-four to forty-eight hours and are replaced by a gray-white pseudomembrane. The lesions usually become secondarily infected and may remain patchy or become confluent and extremely extensive. Frequently, conjunctivitis appears at the same time and may progress to involve the deeper structures of the eye, resulting in partial or total blindness. Bronchitis occurs in the majority of cases and may go on occasionally to bronchopneumonia. These early manifestations are followed later by erythema multiforme, usually of the iris type, with a predilection for the hands and feet but occasionally generalized, and balanitis which originates in or around the urethral meatus. Recovery is complete except for the rare severe ocular

Capt Alfred L. Florman, Medical Corps, Army of the United States, performed the experimental work at the Ninth Service Command Virus Laboratory, and Col. Ralph E. Curti and Lieut. Col. George D. Doroshow, Medical Corps, Army of the United States, contributed helpful suggestions.

TABLE 1.—*Résumé of Cases Compiled from*

Author	Age, Yr.	Sex	Prodromal Symptoms	Skin	Oropharynx	
Blair (1904)	12	Male	?	Generalized maculopapular rash, later iris in type, then pustular	Pseudomembranous stomatitis, with ulceration	Conjunctiv diphtheriti
Barkan (1913)	?	Male	?	Generalized erythema multiforme, with hemorrhagic blebs	Diffuse stomatitis, with vesicles and ulcers	Pseudomem vitis leadi opacities a
Stark (1918)	6	Female	Fever	Generalized erythema multiforme, later iris in type	Diffuse stomatitis	Chronic pse conjunctivi and corneal
Stevens and Johnson (1922)	8	Male	Sore throat, malaise	Generalized erythema multiforme	Vesicles followed by patchy erosions	Purulent co ending in le ulceration
	7	Male	Conjunctivitis	Generalized macular rash, later hemorrhagic scaling	Normal	Purulent co corneal ulce tion of both
Butler (1922)	16	Male	?	Iris lesions on hands and feet	Diffuse stomatitis, with vesicles and erosions	
Wheeler (1929)	8	Male	Cold, malaise and sore eyes and mouth	Generalized macular rash	Scattered membrane in mouth and pharynx	Purulent co then bilater ulceration a
Smith (1929)	9	Male	Cough, malaise and generalized itching rash	Generalized maculopapular rash, with vesiculation and erosion	Pronounced stomatitis with vesiculation	Purulent co
Rutherford (1929)	2	Male	Cold and sore throat	Erythema multiforme on face and forearms	?	Recurring p ous conjunc deep infecti
Bailey (1931)	39	Male	Cold, cough, sore throat, malaise and fever	Generalized erythema multiforme, with hemorrhage and crusting	Diffuse pseudomembrane; crusting of lips	Purulent co corneal ulce
	9	Male	Sore throat, fever, malaise and rash	Generalized erythema multiforme, with hemorrhage and vesiculation	Diffuse ulceration and hemorrhage, then a diffuse pseudomembra	Purulent co pseudomem neal ulcerat
	7	Male	Malaise, pain in extremities and rash	Generalized maculopapular rash, later hemorrhagic	Sore; no mention of findings	Purulent co corneal scar
Ginandes (1935)	5	Male	Malaise, fever and rash	Generalized erythema multiforme, later vesicular, bullous, and hemorrhagic	Vesicles, then pseudomembrane with ulcers; gums involved	Purulent co endophthal left side
Klauder (1939)	7	Male	Cold, fever and sore eyes and mouth	Normal	Moderate stomatitis, w crusting of lips	Purulent co
	13	Male	Cold, cough, malaise and sore mouth and throat	Iris lesions on palms and soles	Vesicles followed by co fluent pseudomembrane	Purulent co
Laszlo (1939)	23	Male	Cold and sore eyes and mouth	Normal	Pseudomembrane (also present in nose)	Purulent co with pseudo
Rosenberg and Rosenberg (1940)	11	Male	Cold, cough, fever, malaise and sore mouth	Erythema multiforme on arms and legs	Pseudomembrane; gum swollen and hemorrha	Purulent co
Ageloff (1940)	4	Female	Fever and rash	Generalized erythema multiforme with iris lesions and bullae	Diffuse ulceration and crusting of lips	Purulent co
Givner and Ageloff (1941)	23	Male	Fever and sore eyes and mouth	Generalized erythema multiforme with iris lesions and bullae	Diffuse pseudomembrane	Pseudomem junctivitis
Levy (1943)	27	Male	Sore throat and rash	Iris lesions	Patchy pseudomembrane	Normal
Murphy (1944)	22	Male	Cough, malaise and sore mouth	Iris lesions on soles, palms and extremities	Vesicles, then confluent pseudomembrane	Micropurulen junctivitis

Eyes	Genital Region	Lungs	White Blood Cell Count	Duration of Fever	Bacteriology	Comment
Conjunctivitis followed by diphtheritic membrane	Membrane over glans	Broncho-pneumonia	?	4 to 6 wk.	Mixed pyogenic organisms in mouth and eyes	Six recurrences; cervical adenopathy on one occasion and involvement of anus and larynx on another
Pseudomembranous conjunctivitis leading to corneal opacities and blindness	Bloody urethral discharge	?	?	?	?	Previous attack 6 mo. before with stomatitis and conjunctivitis
Chronic pseudomembranous conjunctivitis ending in scars and corneal opacities	?	?	?	?	?	Residual blindness
Purulent conjunctivitis ending in left corneal ulceration and scarring	Normal	Normal	4,600	24 days	Mixed pyogenic organisms in mouth and eyes	Partial loss of vision
Purulent conjunctivitis, corneal ulcers and destruction of both globes	Normal	Broncho-pneumonia	?	5 wk.	?	Complete blindness
	?	?	?	?	?	Fourth attack; in next attack had stomatitis plus similar lesions in esophagus and rectum
Purulent conjunctivitis, then bilateral corneal ulceration and scarring	?	?	7,000	?	Mixed pyogenic organisms in eyes	Residual partial blindness
Purulent conjunctivitis	?	Broncho-pneumonia	11,000	7 days	Hemolytic streptococci in sputum	Fatal in 7 days; autopsy revealed severe diphtheritic type of inflammation of skin, mouth and respiratory tract
Recurring pseudomembranous conjunctivitis followed by deep infection of both bulbs	Normal	Bronchitis	?	60 days	Mixed pyogenic organisms in eyes	Enucleation of both eyes
Purulent conjunctivitis, then corneal ulceration and scarring	Normal	?	?	3 wk.	Usual organisms in mouth	Residual partial blindness
Purulent conjunctivitis with pseudomembrane, then corneal ulceration and scarring	Normal	Bronchitis	Normal	3 wk.	Staph. aureus in mouth and eyes; culture of the blood sterile	Complete blindness
Purulent conjunctivitis, then corneal scarring bilaterally	Normal	Normal	16,000	18 days	Smears negative for diphtheria bacilli in eyes and throat; culture of the blood sterile	Complete blindness
Purulent conjunctivitis, then endophthalmitis on the left side	Normal	Normal	6,000	10 days	No Vincent's organisms; mixed pyogens in eyes and mouth; cultures of the blood negative	Enucleation of left eye
Purulent conjunctivitis	Normal	Normal	?	7 days	?	Uneventful recovery
Purulent conjunctivitis	Vesicles on glans	Bronchitis	14,800	14 days	No Vincent's organisms in the mouth	Uneventful recovery
Purulent conjunctivitis with pseudomembrane	Pseudomembrane on glans	Normal	16,700	10 days	No Vincent's organisms in the mouth; Staph. albus in the eyes	Uneventful recovery
Purulent conjunctivitis	Normal	Purulent bronchitis	22,000	21 days	No Vincent's organisms in the mouth	Residual bronchiectasis and pulmonary fibrosis
Purulent conjunctivitis	Diffuse vaginal lesions	Normal	20,400	14 days	No Vincent's organisms in the mouth	Biopsy of skin revealed specific inflammation
Pseudomembranous conjunctivitis	Normal	?	?	?	Staph. aureus in eyes; cultures of vesicle fluid in yolk sacs negative	Vesicular lesions in nose; desquamation of nails
Normal	Normal	Normal	9,600	?	?	Uneventful recovery
Mucopurulent conjunctivitis	Vesicles on glans	Normal	13,000	5 days	Eosinophils in oral vesicles	Pseudomembranous rhinitis also present; uneventful recovery

complications, but a patient may have one or more recurrences, as many as fourteen having been reported.

LITERATURE

Twenty-two cases were compiled from sources in the English language. Those reported in foreign literature were not covered extensively (table 1). Von Hebra,[1] in 1866, is generally credited with first having separated erythema exudativum multiforme from the heterogeneous erythemas. This he regarded as a clinical entity characterized by fever, constitutional symptoms and cutaneous lesions. The last were described as dark blue or purplish erythematous macules, later becoming papular or nodular or developing central clearing (erythema iris) or central vesiculation (herpes). In the average case the eruption was present on the dorsa of the hands and feet, but it could spread to the trunk and face in the severer instances. There was a seasonal incidence—in spring and fall—and a tendency to relapse. Later writers enlarged on Hebra's concept. In 1876 Fuchs [2] called attention to ocular involvement by reporting a case with pseudomembranous conjunctivitis associated with a generalized eruption of the herpes iris type and vesicles in the buccal mucous membrane, under the term "herpes iris conjunctivae." The conjunctival involvement ranges from a mild inflammation to a severe membranous form which may lead to ulceration of the cornea and subsequent loss of vision. Kaposi [3] in 1893, in stressing the oral involvement, said:

> With the appearance of the skin eruption there may be seen similar lesions, reddish spots, papules and vesicles on the mucous membrane of the mouth and throat over which the epithelium rapidly becomes turbid and is elevated in the form of membranes and shreds so that painful wounds arise. Rarely, the epiglottis, larynx, vulvovaginal and urethral mucous membranes are attacked.

In his book "Histopathology of Diseases of Skin," in 1896, Unna [4] echoed Hebra's criteria for diagnosis. An epidemic form of the disease in Turkey was reported by von Duhring in 1896.[5]

In the American literature Whitehouse [6] in 1900 gave the first fairly good description of the subject while discussing erythema exudativum

1. von Hebra, F.: Diseases of Skin, London, New Sydenham Society, 1866, vol. 1.

2. Fuchs, E.: Herpes Iris Conjunctivae, Klin. Monatsbl. f. Augenh. **14**:333-351, 1876.

3. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, ed. 4, Vienna, Urban & Schwarzenberg, 1893.

4. Unna, P. G.: Histopathology of Diseases of Skin, translated by N. Walker, edited by C. H. Fagge, New York, Macmillan & Co., 1896, p. 21.

5. von Duhring, E.: Bietrag zur Lehre von den polymorphen Erytheman, Arch. f. Dermat. u. Syph. **35**:211-323, 1896.

6. Whitehouse, H.: Twentieth Century Practice of Medicine, New York, William Wood & Company, 1900, vol. 5, p. 50.

multiforme of the herpes iris type. He reported that the disease might begin on and be confined to a mucous membrane and emphasized the involvement of the mouth and pharynx and associated pain and dysphagia.

Blair [7] in 1904 published a report of a classic case which leaves little to be added. He emphasized the tendency to recurrence. His patient was a 12 year old boy whose illness began in May with many "sores" covering one third of the buccal, sublingual, gingival and palatal surfaces. These were ulcerated but covered with a diphtheria-like membrane. Salivation was pronounced, and swallowing was difficult. On the sixth day a rash and conjunctivitis appeared. The temperature was high and continued so. The cutaneous lesions became iris type or even bullous, hemorrhagic and, finally, crusted. A "diphtheria-like" condition developed in the eyes. The illness lasted one month, and recovery was accompanied with scarring in the eyes and mouth. The next two attacks occurred in May 1900 and June 1901. The fourth attack, in March 1903, lasted six weeks and was the severest. This time, confluent membrane formed in the mouth and then spread to the nasal passages, nasopharynx, larynx and, eventually, trachea, simulating laryngeal diphtheria. The conjunctivas became involved, and then membrane formed around the anus, glans penis and urethra. On the eighth day successive crops of generalized iris lesions began to appear. In the fourth week bronchopneumonia developed, lasting five or six days. Thereafter, convalescence and recovery were uneventful. The cutaneous lesions healed but left a coppery discoloration behind, which persisted for months. The fifth and sixth attacks occurred in the same year but were much milder. (No mention is made of the drugs used.)

In a brief report, Barkan [8] in 1912 reported a case of the condition in a male, age not mentioned, who recovered from two attacks, the first with conjunctivitis and stomatitis and the second, fifteen months later, with fever, generalized erythema multiforme, stomatitis, bloody urethral discharge and severe conjunctivitis ending in bilateral corneal opacities. A similar condition in a 6 year old girl was reported by Stark [9] in 1918, resulting in membranous conjunctivitis lasting four years and leaving residual corneal opacities.

In 1922 Stevens and Johnson,[10] under the impression that they were describing a new entity, reported 2 cases under the diagnosis of eruptive fever with stomatitis and ophthalmia. However, their findings did not

7. Blair, L. E.: A case of Recurring Membranous Stomatitis, Associated with Erythema Exudativum Multiforme (Hebra), M. Rec. **65**:729-732, 1904.

8. Barkan, H.: Herpes Iris of the Conjunctiva: Report of a Case, Arch. Ophth. **42**:236-240, 1913.

9. Stark, H. H.: Membranous Conjunctivitis of Over Four Years' Duration, Am. J. Ophth. **1**:91-94 (Feb.) 1918.

10. Stevens, A. M., and Johnson, F. C.: New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:526-533 (Dec.) 1922.

differ significantly from those of Whitehouse, Blair, Barkan, Stark and others. The cutaneous lesions were generalized in both cases and consisted of red to purple macules, changing to papules, which later became hemorrhagic (in 1) and then crusted and cleared, leaving faint brownish pigmentation for some time. The rash in the second case lasted for five weeks, the palms and soles being involved, which is unusual. Lesions in the mouth were absent in case 2 and apparently of little significance in case 1. Ocular involvement was severe, starting with purulent conjunctivitis and ending with a corneal scar in case 1 and panophthalmitis in case 2, with rupture of both globes and total blindness. From an etiologic standpoint, there was no history of ingestion of drugs. Smears and cultures of material from the mouth and eyes revealed mixed infection. Cultures of the blood were sterile in case 1. The authors stated:

> Erythema multiforme, from some unknown toxic cause, was proposed as a diagnosis, but this is unsatisfactory from the character and distribution of the lesions, the lack of subjective symptoms, the prolonged high fever, and the terminal heavy crusting. . . . Finally, we have been impressed by the striking picture presented by these cases. Here is a syndrome of dramatic onset, with fever, conjunctivitis and cutaneous eruption. The child is prostrated, the mouth and tongue are inflamed and raw, the eyelids are swollen and pus streams from the eyes. There is a course of three or more weeks of high fever, with leukopenia. The eruption, unlike any hitherto described, comes out progressively, for two weeks or more, matures and resolves in horny crusts, in the order of its appearance. The temperature falls with this resolution of the skin lesions. This syndrome suggests strongly an infectious disease of unknown etiology. We believe that this condition deserves to be considered a definite clinical entity.

Butler [11] in 1922 observed a 16 year old boy in four attacks of diffuse stomatitis characterized by vesicles and diffuse erosion. On one occasion similar lesions were present in the esophagus and rectum. Involvement of the skin was an accompanying finding only once, when iris lesions appeared on both surfaces of the hands and feet.

In 1925 Baader [12] described 7 cases of what he termed "dermatostomatitis." These cases apparently fall into the group under discussion, since there were high temperature, systemic symptoms, conjunctivitis, balanitis, rhinitis and severe membranous stomatitis. The cutaneous lesions were frequently of the iris type, but the author hesitated to place his cases in the group of cases of eruptive fever since the eruptions did not occur on the sites of predilection described by Hebra.

An instance of severe purulent conjunctivitis followed by corneal ulceration and finally scarring was reported by Wheeler [13] (1929) in

11. Butler, J.: Erythema Multiforme Confined to Mucous Membranes, Arch. Dermat. & Syph. **6**:1-5 (July) 1922.

12. Baader, J.: Dermatostomatitis, Arch. f. Dermat. u. Syph. **149**:261-268, 1925.

13. Wheeler, J. M.: Destructive Purulent Ophthalmia Accompanying an Eruptive Fever with Stomatitis: Report of a Case, Tr. Am. Acad. Ophth. **34**:179-180, 1929.

an 8 year old boy. The onset was respiratory in type and was followed by a generalized macular eruption and the appearance of scattered, patchy pseudomembrane in the mouth and pharynx.

In 1929 an unusual fatal case of erythema multiforme in a 9 year old boy was reported by Smith.[14] The illness ran its course in six days, with high temperature, a rapidly spreading generalized maculopapular eruption resulting in vesicles and bullae up to 5 cm. in diameter, oral involvement similar to that of the skin, severe purulent conjunctivitis and, finally, bilateral bronchopneumonia. There was no known exposure to contagion or drugs. There were 11,200 leukocytes per cubic millimeter of blood, culture of the blood was sterile and the sputum contained a type II pneumococcus. Findings at autopsy were inconclusive. The diagnosis of erythema multiforme was considered most likely.

Ophthalmologists have long been interested in membranous conjunctivitis, seeing it in association with a variety of contagious and dermatologic diseases, including erythema multiforme.[14a] Bailey[15] (1931), in reporting 3 cases of the latter with residual partial or complete blindness, pointed out as the main clinical features: (1) an onset characteristic of acute infection, with chilly sensations, fever, headaches, anorexia, malaise and frequent pain in the joints; (2) decided inflammatory changes in the conjunctivas and corneas, eventuating in serious visual impairment and often in total destruction of the bulb; (3) an intense pseudomembranous inflammation of the various surfaces of the lips, tongue, palate, oropharynx and, occasionally, of the nares, larynx, bronchi and even the vagina and (4) widespread polymorphous eruption of the skin. In discussing the ocular complications, Bailey emphasized the insidious progression from hyperemia to destruction of tissue, often necessitating enucleation.

Ginandes[16] in 1935, while reporting a typical case, endeavored to break down Stevens and Johnson's rigid insistence on the type of the cutaneous lesions and other characteristics of the disease. He insisted:

> The slight variations in the nature and duration of the cutaneous lesions and the difference in the degree of buccal and ocular involvement should not prevent one from recognizing the identity of the more important clinical manifestations. Dermatologists have frequently emphasized that the character of the cutaneous

14. Smith, C. A.: Unusual Case of Erythema Multiforme, Tr. Univ. Michigan Pediat. & Infect. Dis. Soc., 1929, pp. 63-67.

14a. Rutherford, C. W.: Membranous Conjunctivitis with Loss of Eyeballs: Report of Cases, J. A. M. A. **93**:1779-1784 (Dec. 7) 1929.

15. Bailey, J. H.: Lesions of Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, Arch. Ophth. **6**:362-379 (Sept.) 1931.

16. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson), Am. J. Dis. Child. **49**: 1148-1160 (May) 1935.

lesions is markedly altered by the degree of exudation. Thus, a certain eruptive fever that may cause macular or papular lesions in one patient may give rise to vesicular or bullous lesions in another. . . . Similarly the severity of the ocular manifestations, as has been pointed out by Rutherford, may simply be the expression of the degree of reaction.

It is significant that heretofore such cases have been described in the main by the dermatologists and the ophthalmologists. In the last six years Edgar and Syverton,[17] Laszlo,[18] Rosenberg and Rosenberg,[19] Ageloff,[20] Givner and Ageloff,[21] Levy [22] and Murphy [23] have reported cases of this syndrome. It is interesting to note that Murphy considered the disease to be "definitely in the pediatric sphere."

Ectodermosis erosiva pluriorificialis, an old and still confusing term for this disease, originating with Fiessinger and Rendu [24] in 1917, was reintroduced by Klauder [25] in 1937. He considered it to be a variant of erythema multiforme and traced its similarity to human foot and mouth disease but was unable to show any relationship by experimental means. He covered the literature thoroughly and expressed the opinion that erythema exudativum multiforme as described by Hebra is probably a specific disease of relapsing nature. He subdivided the disease into several clinical varieties, mainly the Hebra type, involving the skin pri-

17. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. **12**:151-159 (Feb.) 1938.

18. Laszlo, A. F.: Acute Pseudomembranous Infections Involving Eye, Mouth, Throat and Urethra, Laryngoscope **49**:208-216 (March) 1939.

19. Rosenberg, L., and Rosenberg, J.: Erythema Exudativum Multiforme (Hebra), with Conjunctivitis and Stomatitis, Arch. Dermat. & Syph. **41**:1066-1072 (June) 1940.

20. Ageloff, H.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Eyes and Mouth (Stevens-Johnson Disease): Report of Case, New England J. Med. **223**:217-219 (Aug. 8) 1940. Andrews, G. C.: Diseases of Skin, Philadelphia, W. B. Saunders Company, 1938.

21. Givner, I., and Ageloff, H.: Stevens-Johnson Disease with Complete Visual Recovery, New York State J. Med. **41**:1762-1765 (Sept. 1) 1941.

22. Levy, A. T.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Mouth (Stevens-Johnson Disease), J. Am. Dent. A. **30**:287-288 (Feb.) 1943.

23. Murphy, R. C., Jr.: Eruptive Fever Involving Mouth and Eyes (Stevens-Johnson Disease), New England J. Med. **230**:69-71 (Jan. 20) 1944.

24. Fiessinger, N., and Rendu, R.: Sur un syndrome caracterise par l'inflammation simultanée de toutes les muqueses externes coexistant avec uno eruption vesiculeuse des quatre membres, non douloureuse et non recidivante, Paris méd. **23**:54-58, 1917.

25. Klauder, J. V.: Ectodermosis Erosiva Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exsudativum Multiforme, Arch. Dermat. & Syph. **36**:1067-1077 (Nov.) 1937.

Fig. 1.—*A*, late pseudomembrane on the tongue. *B*, crusting of the lips, associated with conjunctival injection. *C*, iris lesions on the thighs.

TABLE 2.—*Scope of Erythema Exudativum Multiforme* (Reprinted from Klauder [25])

Erythema Exudativum Multiforme (Hebra)	Toxic Erythema Resembling Erythema Exudativum Multiforme
(Probably a specific disease, relapsing, involving the skin and mucous membranes. Cutaneous lesions: erythema of variable shape, papules, nodules, vesicles, bullae and hemorrhagic macules. Distinctive lesions: annular erythema with central clearing, erythema iris and herpes iris)	(A cutaneous reaction to various causes. Cutaneous lesions: erythema, vesicles, bullae, angioneurotic edema, urticaria and purpura)

Types Affecting the Mucous Membranes						
Hebra Type	Ocular	Nasal	Oral	(Ectodermosis Erosive Pluri-orificialis)	Severe Type (Stevens-Johnson)	
Commonest; eruption favors areas of predilection, with or without constitutional symptoms or involvement of mucous membrane	Vesicles; simple inflammation; membranous conjunctivitis	Simple inflammation	Vesicles; erosions; diffuse stomatitis	Fever; constitutional symptoms; vesicular eruption on hands and feet; conjunctivitis; stomatitis and rhinitis	Fever; constitutional symptoms; hemorrhagic macules; crusting; scaling; stomatitis; membranous conjunctivitis; leukopenia	1. Systemic infection 2. Drug eruption 3. Serum sickness associated with visceral disease 4. Osler's erythema group 5. Libman-Sacks syndrome 6 Toxic erythema described as: (a) Urticaria perstans annulata et gyrata (b) Erythema multiforme perstans (c) Erythema urticatum (d) Erythema bullosum

TABLE 3.—*Résumé of Cases*

Case	Age, Yr.	Entry	Prodomal Symptoms	Stomatitis	Conjunctivitis	Balanitis	Dermatitis	Days of Fever	Involvement of the Respiratory Tract	Bacteriologic Studies
1	27	10/13/41	Erosion of glans penis and dysuria	Patchy pseudomembrane	None	Erosion about meatus	None	3	None	No Vincent's organisms in the mouth
2	22	1/19/42	Cold and cough	Patchy pseudomembrane	Catarrhal	.....	.....	9	Bronchopneumonia of the lower lobe of the right lung	A few Vincent's organisms in the mouth
3	26	2/15/42	Cold and cough	Vesicles, then patchy pseudomembrane	Mucopurulent	None	Iris lesions on palms, soles and forearms	6	Dry cough	Not done
4	27	2/26/42	Cold	Patchy pseudomembrane	None	None	None	1	None	Not done
5	21	3/ 4/42	Photophobia, cold and cough	Vesicles, then patchy pseudomembrane	Purulent	Vesicles, then pseudomembrane	None	7	Productive cough	Not done
6	22	3/12/42	Cold and fever	Vesicles, then patchy pseudomembrane	Mucopurulent	None	None	4	None	Vincent's organisms present in the mouth
7	21	3/19/42	Cold and cough	Vesicles, then patchy pseudomembrane	Catarrhal	None	None	0	None	No record
8	27	4/24/42	Cold, cough and photophobia	Patchy pseudomembrane	Catarrhal	Pseudomembrane	None	0	None	Not done
9	25	5/11/42	Cold, cough, fever and malaise	Vesicles, then confluent pseudomembrane	Mucopurulent	Erosion and maceration of glans	None	12	Productive cough; rhonchi in chest	Staphylococci and streptococci in the mouth, no Vincent's organisms; hemolytic Staph. aureus in eyes
10	24	5/24/42	Cold, cough, fever and photophobia	Confluent pseudomembrane	Catarrhal	Erosion about meatus	None	7	Productive cough	Not done
11	28	6/ 4/42	Cough, sore throat, fever and headache	Vesicles, then patchy pseudomembrane	Catarrhal	Pseudomembrane	None	10	None	Not done
12	24	6/ 8/42	Cold and cough	Vesicles, then patchy pseudomembrane	Mucopurulent	Pseudomembrane	Maculopapules on forearms	9	Productive cough	No record
13	24	1/ 2/43	Cold and cough	Vesicles, then patchy pseudomembrane	None	Erosion about meatus	None	0	None	Not done
14	21	1/ 3/43	Cold, cough and sore throat	Vesicles, then patchy pseudomembrane	None	None	None	1	None	Not done
15	30	2/24/44	Cold and cough	Vesicles, then patchy pseudomembrane	None	Erosion and maceration of glans	None	0	None	Not done
16	31	2/14/44	Sore throat, cold and cough	Vesicles, then patchy pseudomembrane	Purulent	Erosion, maceration and secondary infection	None	8	None	Hemolytic Staph. aureus in the eyes
17	18	4/ 2/44	Cough and fever	Patchy pseudomembrane	Catarrhal	Pseudomembrane	Iris lesion on palms and soles	9	Productive cough; rales in the lower lobes of both lungs	Streptococci and Staph. aureus in the mouth; no Vincent's organisms
18	24	10/13/44	Cough, cold and fever	Vesicles, then patchy pseudomembrane	Catarrhal	None	None	7	Productive cough; patchy pneumonia in the lower lobe of the right lung	Alpha streptococci and nonhemolytic Staph. aureus in the mouth; no Vincent's organisms
19	24	1/18/45	Cold, cough, aches, malaise and fever	Vesicles and bullae; later diffuse pseudomembrane present	Severe purulent; later pseudomembrane present	Bullae; later pseudomembrane formed also on prepuce and scrotum	Iris lesions on extensor surfaces of arms and legs	16	Severe bronchitis with asthma; 500 cc. of sputum daily	Mixed organisms in mouth, eyes and genitals; no Vincent's organisms
20	18	1/30/45	Cough for 3 wk.; burning eyes and [illegible] to mouth	Patchy pseudomembrane	None on entry; gave history of	Slight erosion of meatus	None	1	Slightly productive cough; few coarse rales in lower [illegible]	No Vincent's organisms in mouth

marily; the type called ectodermosis pluriorificialis erosiva, and, finally, the Stevens-Johnson type. His cases fall into the second group, as do most of those described in this article, the condition being less severe than the Stevens-Johnson type in that the ocular manifestations do not progress beyond purulent conjunctivitis and the cutaneous lesions are usually limited to the extremities and are vesicular rather than hemorrhagic or maculopapular (table 2).

PRESENTATION OF A CASE

Table 3 presents a résumé of the cases in this series. A typical case is presented here.

CASE 19.—E. R., aged 24, entered the hospital on Jan. 18, 1945, with a history of backache for two months and headache, cough and fever for two days. In addition, he had noted nausea and vomiting for the previous two days. There was no relevant past history. The only medicament taken had been a prophylactic dose of 2 Gm. of sulfadiazine three months before.

On initial examination the only findings indicative of the disease were moderate conjunctival injection and an oral temperature of 102 F.

Course.—During the next week the temperature reached 102 F. daily. Medication included acetylsalicylic acid, acetophenetidin, caffeine and codeine. Nothing new developed until January 24, when many vesicles appeared in the mouth, some hemorrhagic. During the next several days the patient became toxic and the daily temperature rose to 104 F. Cough increased and became productive of much thick, mucopurulent sputum. The patient complained of substernal distress, and sibilant rales and expiratory rhonchi developed throughout both fields of the lungs. New vesicles and bullae, up to 1.5 cm. in diameter, appeared in the mouth until January 28 and then ruptured and gave way to a diffuse pseudomembrane which covered the lips, buccal mucosa, under surface of the tongue, palate and pharynx. Patchy membrane was present on the gums, which, however, did not show swelling, erythema, retraction or marginal ulceration at any time. The voice sank to a whisper, but laryngoscopic examination could not be tolerated. Compression of the larynx elicited pain. Swallowing became impossible, and for one week the patient was maintained on fluids administered intravenously, plasma and two blood transfusions. Some relief from soreness of the mouth was obtained by the use of sprays of tetracaine hydrochloride and irrigations with potassium permanganate.

Coincident with the onset of the stomatitis the conjunctivas became inflamed and drained purulent material. By February 29 a thin gray pseudomembrane appeared at the base of both lower tarsal sacs. At the same time small patches of pseudomembrane were evident on the turbinates of the nose bilaterally. Previously there had been nasal injection, crusting and occasional nosebleeds.

The skin finally became involved on February 27, when scattered erythematous macules averaging 1 cm. in diameter appeared on the extensor surfaces of the knees and elbows. These gradually became papular, and eventually developed either a central vesicle or a central area of clearing. A few new lesions made their appearance in the next several days, also involving the extensor surfaces of the ankles, thighs and upper parts of the arms. These persisted for seven to ten days, then crusted and finally left brown areas of pigmentation. Changes on the penis began at the same time, with injection and maceration of the glans followed by formation of bullae and, eventually, pseudomembrane. Interestingly, spread due to contact occurred on the prepuce and adjacent scrotum.

The patient continued to have a remittent temperature up to 104 F., which gradually subsided by March 2. Bronchial involvement was striking, at times 500 cc. of mucopurulent sputum being produced daily. Because of the large amount of sediment in the sputum, it was suspected that considerable desquamation was occurring in the bronchial mucosa. By February 30 there was noticeable general improvement. The patient took 1,300 cc. of bland fluids by mouth. By February 2 some peeling of the oral membrane had occurred and the tarsal membrane was gone. By February 5 the eyes and nose were clear, the cough was minimal and a soft diet was being taken. In the next ten days oral and penile pseudomembranes gradually disappeared. The tongue had desquamated completely, leaving a red, smooth dorsal surface.

A total of 500,000 units of penicillin was given intravenously from February 24 to February 29, without apparent effect. Penicillin ointment was used on the penis and in the eyes.

Laboratory Data.—The white blood cell count averaged 10,000 per cubic millimeter, but on one occasion it reached 15,000, with a fairly normal differential count. The urine was normal at all times. The mouth contained no Vincent's organisms. Smears and cultures revealed a variety of organisms, including staphylococci and diphtheroid organisms. From the eye were cultured Staphylococcus aureus and two strains of diphtheroid bacilli. From the sputum were obtained Staph. aureus, Streptococcus viridans, Neisseria catarrhalis and Hemophilus influenzae. Decided phagocytosis of H. influenzae and gram-positive cocci were noted for several days. On the penis there were diphtheroid bacilli and Staph aureus. Culture of the blood was sterile.

COMMENT ON CASES

Discussion here will be limited to a few pertinent features illustrated by the histories of the cases in this series (table 4).

None of the patients presented serious ophthalmologic problems. Their illnesses were milder in general, although in cases 9 and 19 the condition was as severe as many of those reported elsewhere. In 2 patients stomatitis was the only finding. One man was admitted to a ward for patients with conditions within the genitourinary tract because of dysuria and penile lesions, which were his initial complaints. Oral symptoms did not appear until three days later. Regarding seasonal incidence, table 1 indicates that in 90 per cent of the cases the condition occurred from January to June inclusive, as originally reported by Hebra and confirmed by others. The age incidence ranged from 18 to 31 years, considerably higher than in any previous experience, demonstrating that this is not a pediatric problem exclusively but one which concerns the internist as well.

In the search for causative factors, ingestion of drugs was considered. In 3 instances acetylsalicylic acid was taken during the prodromal period, and in 2 codeine was taken. Nothing in the past histories of the patients indicated any idiosyncrasy to these substances. Phenolphthalein was considered, but no one admitted taking it in any form and it was not available in the local medical supply. Several had received 2 Gm. of

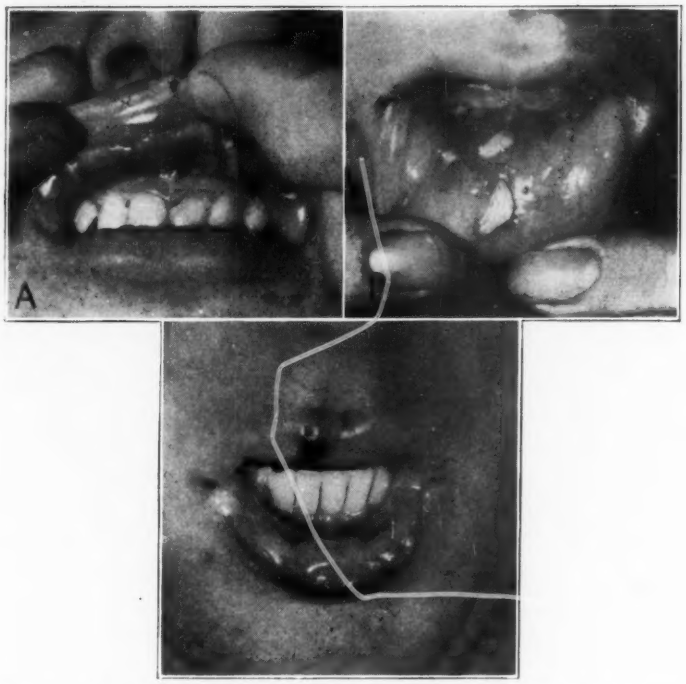

Fig. 2.—*A* and *B*, late pseudomembrane on the buccal surfaces. *C*, late pseudomembrane on the lips.

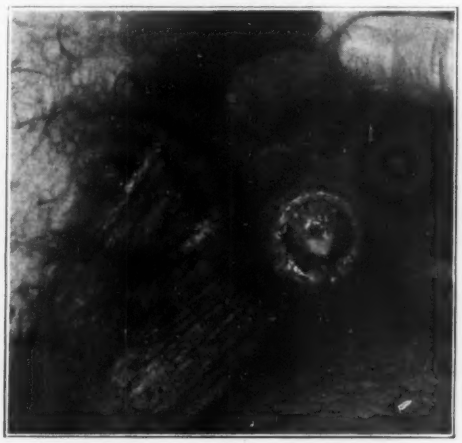

Fig. 3.—Erosion, maceration and pseudomembranous involvement of the penis.

sulfadiazine three to four months before. Two had sulfonamide therapy during the course of the disease. The men were all well nourished and healthy and had had at least several months of adequate diet in the service.

TABLE 4.—*Incidence of Symtoms and Findings*

	Literature	Present Series
Total number of cases	22	20
Prodromal respiratory symptoms		
Present	10	19
Absent	?	1
Fever and duration		
Afebrile	?	4
1 week	3	9
2 weeks	4	6
3 weeks	5	1
4 weeks and more	3	0
Not recorded	7	..
Cutaneous lesions		
Vesicular or bullous	13	3
Maculopapular	7	1
None	2	16
Oral involvement		
Vesicular	6	13
Vesicular with ulceration	4	0
Pseudomembranous	7	7
"Stomatitis"	2	0
None	3	0
Ocular involvement		
Conjunctivitis		
Catarrhal	0	7
Purulent	7	5
Pseudomembranous	3	2
Severe complications from corneal ulceration to panophthalmitis	10	0
None	2	6
Pulmonary involvement		
Bronchitis	4	7
Pneumonia	3	2
None	15	11
Genital involvement		
Balanitis	5	13
Urethral discharge	1	0
Vaginitis	1	0
None	15	7
Adenopathy		
Cervical	3	0
Generalized	1	0
None	18	20
Recurrent attacks	3	2
White blood cell count		
Leukocytosis	6	10
Leukopenia	1	0
Normal	5	5
Not recorded	10	5

Symptoms in the respiratory tract initiated the illness in 19 out of 20 cases as contrasted with 10 of the 22 cases in the literature. These varied from a cold in the milder instances to dry or productive cough, sore throat and generalized malaise in the more severely ill patients. Only 1 patient complained of the rheumatic pains that have been men-

tioned occasionally in the literature. The foregoing symptoms usually were of short duration. Three patients were admitted to wards for patients with conditions within the respiratory tract. Findings were minimal and limited to nasal congestion and discharge, slight redness of the throat and some tarsal conjunctival injection. One patient improved and was discharged after three days, and then acute soreness of the mouth, with vesiculation, developed several hours later. In the other 2 oral symptoms and signs developed on the second and third days respectively in the hospital. All other patients entered the hospital with lesions on the mucous membrane well established. In 7 cases bronchitis persisted, as manifested by cough productive of mucoid to purulent sputum and coarse rales and rhonchi usually in the bases of the lungs. In 1 unusual case 500 cc. of viscid, mucopurulent, blood-tinged sputum was collected in one day. In addition, moderate broncho-spasm was present for several days. In 2 other patients patchy broncho-pneumonia developed in the lower lobe of the right lung. Fever occurred in 16 cases and was of an irregular type, the temperature reaching 104 F. and lasting sixteen days in 1 patient.

Conjunctivitis, encountered in 14 cases, was usually present from the onset and involved, in the main, the tarsal portion. The membrane became reddened and velvety, and in 5 patients a mucoid to purulent discharge ensued. Appearing as a late manifestation, a linear, fairly adherent, paper-thin, gray-white pseudomembrane was found at the base of the lower tarsal sacs in 2 patients.

A few salient features of the oral manifestations deserve emphasis. These early observations were constant in this series, while absent in 3 of the cases in the literature. Sites of predilection in decreasing order of frequency were the inner aspects of the cheeks and lips, palate, under surface of the tongue, vermilion border of the lips, fauces and, lastly, superior aspect of the tongue. Redness was never an initial symptom, and swelling or edema was never present. Vesicles would appear rapidly and run their course to rupture in twenty-four hours. They were usually round to oval, transparent and extremely superficial and averaged 5 mm. in diameter, although at times bullae up to 2 cm. in greatest diameter replaced them. Within forty-eight hours the ragged and wrinkled external shells plastered down to form gray-white membrane which became secondarily infected, dull, covered with viscid slime and fetid in odor. In the severe conditions, in which a confluent membrane extended from lips to fauces, pseudomembrane appeared, without prior vesiculation, to fill the spaces between ruptured and intact vesicles. Salivation became progressively more notable. Extreme discomfort, total inability to swallow, great pain on opening the mouth or protruding the tongue, cracking and bleeding of the lips and secondary formation

of crust were striking. Examination of the posterior part of the pharynx proved impossible in these cases. Unfortunately laryngeal examination was not done in the healing stage. Aphonia and laryngeal tenderness indicated local involvement in 1 patient. Recovery began within nine to fourteen days. The pseudomembrane became clean and glistening, and oval red patches of new mucous membrane appeared after desquamation. Soreness decreased, and swallowing became easier. Within a week or two the membrane progressively peeled off, erythema disappeared and finally the last patches disappeared from the areas opposing the teeth.

The genital manifestations were interesting in that they paralleled those of the mouth in character. They usually appeared several days after the oral lesions. Genital involvement was noted in 13, or 65 per cent, of the patients as contrasted to only 6, or 28 per cent, in the literature. Reported incidence of these manifestations was increased by alertness for their presence and repeated examination for them. Frequently, only light redness and stickiness were noted about the meatus, with initial dysuria. Inflammation spread locally. Vesicles and pseudomembrane covered the glands in a patchy or confluent manner in the severer conditions. In 1 patient what seemed to be a spread due to contact occurred on the free margin of the redundant foreskin in ring fashion. From here, areas of maceration and oozing appeared on the anterior portion of the scrotum. Usually, however, the process was confined to the glans.

Iris lesions were the only dermal manifestation. These were scattered over the extremities and usually appeared in the second to third week of illness.

Perianal or intestinal involvement was not seen. In 1 patient small patches of pseudomembrane were present on the nasal septum for several days.

With as extensive an inflammatory process as occurred in the mouths of some patients, it is at first rather surprising that cervical adenopathy was not found at all in this series. This may be explained by the confinement of the process to the epithelial barrier as contrasted to herpetic stomatitis, in which ulceration leads to the consistent finding of regional adenopathy.

Bacteriologic examination of the various exudates and secretions revealed the usual mixed flora indigenous to the respective areas. The urine was normal in all the patients. In 10 leukocytosis was found, ranging from 12,000 to 24,000 cells, and in none was there leukopenia. Stevens and Johnson, because of 1 case, suggested the latter finding as a prerequisite feature for diagnosis, but this was later refuted by Ginandes. Results of a biopsy of skin taken from the patient in case 19 are

reproduced elsewhere and illustrate the changes described by McCarthy.[26] Common values in blood chemistry were checked in some of the patients. No significant alterations were noted except in the chloride metabolism, conservation of the chloride content of the body being observed. Of 12 patients, 3 were found with initial blood values below 400 mg. per hundred cubic centimeters, namely 366, 360 and 380. Total chloride content in the urine dropped from a normal of 5 to 15 Gm. in a twenty-four hour period to less than 1 Gm. Some chloride was lost in the saliva, values up to 2.6 Gm. in twenty-four hours having been reached. The contraction in the chloride economy is undoubtedly largely due to decreased intake because of dysphagia and loss through perspiration.

PATHOLOGY

The best description of the microscopic changes in the skin in erythema exudativum multiforme has been given by McCarthy. Essentially, there is an acute inflammatory process in the epidermis, characterized by edema, congestion and hemorrhage followed by round cell infiltration and, finally, exudation of fluid splitting the cell layers to form vesicles, bullae and sloughs. Bullous lesions here are identical clinically and histologically with those of pemphigus, and the two can be differentiated only by their clinical courses. McCarthy concluded that "we are dealing with a generalized infectious process producing a toxin that is circulated in the blood stream. The histological findings bear this out, and we cannot agree with the view that this is a primary disease of the epithelium."

No deaths have been reported in the literature in the English language except for Smith's questionable instance. Dr. Carl Weller was unable to make a specific diagnosis at autopsy in this case but suggested that because of the apparently spontaneous nature of the eruption of the skin and mucous membrane the condition might be in the class of epidermolysis bullosa. Microscopic examination revealed congestion and edema of the brain, spinal cord, bronchial nodes, thymus, spleen, pancreas, liver and kidneys. Various stages of inflammation, with formation of pseudomembrane, were present in the larger bronchi, tongue, pharynx, larynx and esophagus. The skin showed bullous lesions, with desquamation and superficial ulceration. The changes were sharply limited to the epidermis and upper part of the corium. Bilateral severe purulent bronchitis and bronchopneumonia were present. A streptococcus of unspecified type was found in the upper respiratory tract and esophagus and was considered to be possibly a secondary invader.

The European literature, cited by Blair, includes fatal cases reported by Hebra, Grigorow, Leloir, Hanke[27] and others. No mention can

26. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

27. Hanke, V.: Der Herpes iris des Auges, Arch. f. Ophth. **52**:263-284, 1901.

be found of results of histologic studies of the oral lesions, but, from the clinical similarity in onset and progression to those of the skin, the process is presumably similar. That similar lesions of the larynx, esophagus and rectum can occur has been mentioned by Blair and also by Butler. No reports of microscopic studies of the ocular manifestations were found.

Thus, in summary, there are no distinctive pathologic changes found in erythema exudativum multiforme. Histologic changes in the skin are fairly typical but not specific. Visceral involvement is varied and inconstant, ranging from diffuse inflammatory to pseudomembranous change.

PATHOGENESIS

Investigation of etiology has been haphazard and much neglected. Bacteriologic studies have revealed nothing significant. The cutaneous lesions are usually sterile or contaminated by the staphylococcus. Smears and cultures of material from the mouth and pharynx usually reveal a mixture of flora but a surprising absence of Vincent's saprophytes. Pyogenic organisms are frequently found in the conjunctival discharge and, in a secondary role, probably account for much of the more serious ocular complications. Cultures of the blood are disappointing.

Several investigators have tried inoculation of animals, without significant result. Givner and Ageloff attempted culture of vesicle fluid in yolk sacs. Edgar and Syverton injected similar fluid into guinea pigs, rabbits and mice by all routes. After intravenous administration, 2 rabbits died in anaphylactic shock. Transfer from these animals to others was unsuccessful.

None of the patients who were specifically questioned gave any history of prior ingestion of drugs.

EXPERIMENTAL WORK

With the helpful cooperation of Capt. Alfred C. Florman, Medical Corps, Army of the United States, and the Ninth Service Command Laboratory, attempts were made to establish viral causation. Ideally, isolation of the virus from fluid in the vesicles should be attempted. However, the oral vesicles are so transitory that this did not prove feasible. After much fruitless waiting, it was decided that saliva taken from the patient in case 19 at a time when many freshly ruptured vesicles were present in the mouth would be used for studies on inoculation. The experimental work is summarized here.

I. *Attempts at Isolation with Saliva from the Patient in Case 19.*—Work was started on Jan. 30, 1945, when the frozen, stored specimen of saliva was thawed, diluted 1 to 5 with 2 per cent rabbit serum and inoculated onto the corneas of 3 rabbits. No reaction occurred during eleven days of observation.

The remainder of the saliva was passed through a Mandler 6 filter, and a portion was inoculated intracerebrally on two occasions into each of two groups of 6 Swiss mice. These mice were followed for twenty-one days, but no apparent disease developed.

Some filtrate was also inoculated by the Burnet technic onto the chorioallantoic membrane of ten to twelve day embryonated chick eggs. Three separate series, the original filtrate being used, were studied. The first time, five serial passages were carried out at three to four day intervals; the second time, three serial passages were done, and the third time, fifteen serial passages were completed. These involved 92, 27 and 163 eggs repectively. In each series a somewhat similar picture was produced on some of the membranes. However, despite the fifteen serial passages (each time the membranes with the most extensive lesions were passed) this reaction could not be reproduced with any degree of uniformity or predictability.

The lesions consisted of either a relatively large, thickened plaque, usually central and with a crater-like area of necrosis, or a number of small, pinpoint-sized, thickened areas. On microscopic examination these were found to represent varying degrees of ectodermal proliferation. The cells immediately adjacent to the craters or at the center of the smaller plaques were swollen and appeared to contain cytoplasmic vacuoles. In the underlying mesoderm there was some evidence of edema and an increase in eosinophils.

Unfortunately, this type of reaction is not specific. The lesions resemble, in some respects, the reactions produced by some of the viruses as well as those

TABLE 5.—*Result of Examination of Serum*

	Specific Date	Herpes Neutralization	Elementary Body Complement Fixation, Titer
Case 19	1/30/45	Protected against more than 100 MLD	10
	2/10/45	Protected against more than 100 MLD	10
L. A.*	2/24/45	Protected against more than 100 MLD	10
	5/28/45	Protected against more than 100 MLD	
H. U.*	4/16/45	Protected against 30 MLD	
R. U.*	2/24/45	Protected against more than 100 MLD	10

* Later patients, not seen by the author.

which may follow trauma or hemorrhage. In addition, their relationship to the patient's illness remains to be shown, since they could not be inhibited by a specimen of serum obtained during convalescence.

Attempts to identify the responsible agent were made, egg material from various passages being used. Baby and mature rabbits, albino guinea pigs and white rats were inoculated intracerebrally, intracutaneously and on the cornea. Syrian hamsters and cotton rats were inoculated intraperitoneally. In all, 44 mice, 13 rabbits, 2 guinea pigs, 2 white rats, 2 cotton rats and 2 Syrian hamsters were used. No recognizable disease was produced except that in 1 mature rabbit out of 4 whose corneas were scarified and inoculated with material from the second egg passage of the first series keratitis developed. This appeared on the third day and cleared by the sixth day. No encephalitic symptoms were reproduced with this inoculum, which had been stored in the frozen state, or with material from later passage.

In the absence of a more uniformly susceptible laboratory animal, further work on this aspect of the study was discontinued.

II. *Serologic Studies.*—Because of the clinical similarity to herpetic stomatitis, herpes neutralization tests in mice and complement fixation tests for elementary viruses of the body type with the use of a chick embryo antigen (an inactivated suspension of the elementary bodies of the virus of lymphogranuloma venereum) prepared by E. R. Squibb & Sons were carried out. No significant results were obtained. Serums from the persons listed in table 5 were examined.

On an earlier occasion, the following neutralization tests were carried out against serums from the patients in cases 16 and 17 (table 6).

Five mice were used with each mixture of virus dilution and serum. The numbers in table 6 indicate the day of death for each mouse. The virus used had a titer of $10^{-4.4}$ in rabbit serum for a minimum lethal dose for 50 per cent of the animals. The degree of protection in acute and convalescent phases is seen not to be significantly or constantly altered.

DIFFERENTIAL DIAGNOSIS

The diagnosis of erythema multiforme exudativum is relatively simple if the following features are kept in mind. The disease primarily involves squamous and modified squamous epithelium, producing inflammatory

TABLE 6.—*Herpes Neutralization Test*

Final Virus Dilution	Normal Rabbit Pool	Case 16		Case 17		Normal Human Pool
		Acute 2/19/44	Convalescent 3/3/44	Acute 4/2/44	Convalescent 4/19/44	
10^{-1}	2	7	12	13	9	..
	3	—	—	—	—	..
	4	—	—	—	—	..
	4	—	—	—	—	..
	5	—	—	—	—	..
10^{-2}	4	—	9	5	—	—
	4	—	—	9	—	—
	5	—	—	—	—	—
	5	—	—	—	—	—
	7	—	—	—	—	—
10^{-3}	5	—	—	—	2	—
	5	—	—	—	4	—
	6	—	—	—	—	—
	6	—	—	—	—	—
	—	—	—	—	—	—
10^{-4}	5	..	..	..	..	6
	6	..	..	..	..	—
	9	..	..	..	..	—
	12	..	..	..	..	—
	—	..	..	..	..	—
10^{-5}	7	..	..	..	..	8
	—	..	..	..	..	—
	—	..	..	..	..	—
	—	..	..	..	..	—
	—	..	..	..	..	—

changes resulting in erythema, followed by exudation of fluid and ending in vesicles, bullae and pseudomembranes with or without secondary infection. Secondly, the involvement of the skin is a form of erythema multiforme but nevertheless follows a definite pattern of circumscribed, bilaterally symmetric, maculopapular erythema progressing to formation of fluid and regressing through fine crusting to persistent violaceous or brownish pigmentation. The term "multiforme" is confusing and does not apply to the individual patient, whose lesions are uniform throughout. In the author's series the few with involvement of the skin had, with one exception, the herpes iris type, indistinguishable from patient to patient. Thirdly, the lesions on the mucous mem-

brane go through a similar cycle to that in lesions of the skin, although confusion may arise through initial late contact with the patient at a stage when only pseudomembranes are evident. In these instances the patient, on careful questioning, will reveal that his trouble began with "water blisters." A pitfall to avoid is in the description of superficial erosions in the oropharynx as ulcers. True ulcers did not occur in this series or in the majority of cases in the literature. The description of these lesions is often so sketchy that doubt is engendered as to the accuracy of observation when ulceration is reported. However, it is conceivable that in a rare severe condition ulceration from secondary causes may occur.

Hebra's original conception of eruptive fever has been enlarged and beclouded by the much larger group of toxic erythemas popularly called erythema multiforme. These cutaneous reactions are due to a variety of causes, mainly drugs (bromides, cinchophen, common antipyretics, barbiturates, salicylates, phenolphthalein and sulfonamide drugs), and, to a lesser extent, systemic diseases such as rheumatic fever and Libman-Sacks syndrome. The latter is easily eliminated from consideration, but the former is less easily separated from eruptive fever and tends to overlap. In such cases there is usually a history of ingestion of drugs. Erythema tends to become confluent and generalized and frequently remains macular. Urticarial and petechial elements may appear, associated with pruritus. Lesions are usually in the same stage, and there is an absence of prodromes in the respiratory tract. Papular, vesicular and bullous rashes are less frequent. In the severer conditions involvement of the mucous membrane may occur, but it is usually minor and not at all proportional to the extent of the systemic and dermal upset. When the mouth is involved, patchy erythema is the most frequent finding, with vesicles and pseudomembrane occasionally seen. In the eyes there is seldom more than a catarrhal conjunctivitis. Dardinski's [28] recent report of a fatality due to the use of sulfadiazine illustrates the difficulties of diagnosis: During treatment for pneumonia, a generalized sunburn-like erythema, deep conjunctival injection and redness of the oral membrane developed in a 17 year old girl. Several detachable pieces of white membrane later appeared in the posterior part of the pharynx. The course became septic, many large coalescing bullae appeared over the body and death occurred three days after the onset of the rash. The organs were normal at autopsy. Microscopic examination of the skin revealed splitting of the epidermal layers by fluid, congestion and round cell infiltration in the dermis. Similarly, phenolphthalein may cause difficulty by producing bullous and erosive lesions

28. Dardinski, V. J.: Erythema Multiforme Bullosum Following the Use of Sulfadiazine, Am. J. Clin. Path. **15**:28-29 (Jan.) 1945.

in the mouth and on the genitalia, associated with a rash, which occasionally may be erythema multiforme. However, the more characteristic lesion is a fixed maculopapule of polychromatic hue with ill defined borders.

Pemphigus has many similar features, with its bullous involvement of the skin and mucous membrane, but it is easily distinguished by its chronicity, older age incidence, positive Nikolsky sign and dirty, oozing cutaneous lesions.

A number of children with severe attacks of eruptive fever were sent to hospitals for patients with contagious disease, the diagnosis of hemorrhagic measles having been made, but the differentiation from this and other forms of exanthema should present no real problem.

Conjunctivitis, rhinitis and balanitis are present in the rarely observed instances of foot and mouth disease in human beings, along with vesicular lesions on the extremities and in the mouth. However, the mouth is dry and burning, changes are present about the nails of the hands and feet, a virus can be demonstrated readily by inoculation of a guinea pig and, finally, the disease is nonexistent in this country. A number of cases reported as such in the literature, without confirmation by the inoculation of guinea pigs, may have really been cases of eruptive fever, according to Klauder.

The question of vitamin deficiency is occasionally brought up when physicians who are unfamiliar with the syndrome under discussion view the oral lesions. There is no type of known disease due to vitamin deficiency which simulates eruptive fever.

Acute disease of the mucous membrane of the mouth constitutes one of the most confused fields of medical interest and the one most in need of clarification and classification along etiologic and pathologic lines. This need for enlightenment is particularly pertinent to this discussion because of the general tendency to attach the diagnosis of Vincent's infection to most instances of acute stomatitis or gingivostomatitis.

The frequency with which the saprophytic fusiform bacillus and the spirochete Borrelia vincenti are found in normal as well as diseased mouths cautions against the attachment of too much significance to their presence as primary pathogens. Their role relative to this discussion can be dismissed by pointing to a complete lack of experimental evidence as to their ability to attack healthy mucous membrane. Before enumeration of the oral lesions which may be confused with the stomatitis of eruptive fever, it is important to clarify nomenclature and place it on an etiologic rather than descriptive basis. In eruptive fever or in herpetic stomatitis the various terms infectious, catarrhal, aphthous, ulcerative, membranous and pseudomembranous have been used as diagnostic handles, and yet these merely represent various stages in the cycle of conversion of a vesicle into an ulcer. In as recent an authoritative text as

that of "Oral Diagnosis," by Thoma,[29] the descriptive method of classification is still used. The author lists the following types.

Infectious Stomatitis.—Infectious stomatitis is an acute process characterized by edema, swelling of the membrane, regional adenopathy and fever, due to micrococcus or beta streptococcus. (This is an obscure condition and seems not to occur in the present day.)

Ulcerative Stomatitis.—Ulcerative stomatitis occurs in infants and young children and often is due to mixed infection of staphylococci and streptococci. There are fever; reddened, swollen mucous membrane, with ulcers on buccal, gingival and lingual surfaces, and regional adenopathy. (This corresponds best to herpetic stomatitis, to be described later.)

Ulceromembranous Stomatitis.—Ulceromembranous stomatitis seems to differ from the foregoing disease only in that the process starts in the gingival crevices, where the interdental papillae become decidedly swollen, and then spreads over the entire mouth. (This is probably herpetic stomatitis again.)

Membranous Stomatitis.—In membranous stomatitis false membrane forms throughout the mouth and pharynx. It can be detached easily, leaving a raw, bleeding surface. (This corresponds to the late oral phase of eruptive fever.)

In the past ten years Youmans,[30] Perrin Long,[31] Burnett and Williams,[32] Black,[33] Dodd, Johnston and Buddingh [34] and Scott and Steigman [35] have separated a new clinical entity, herpetic stomatitis, from the wastebasket of forms of stomatitis described previously and proved its causation by the virus of herpes simplex. These authors described an acute gingivostomatitis in infants and a few adults, isolated the virus by inoculation into the corneas and brains of rabbits, proved its identity with the herpes virus by protection tests on animals and demonstrated

29. Thoma, K. H.: Oral Diagnosis, with Suggestions for Treatment, Philadelphia, W. B. Saunders Company, 1943.

30. Youmans, J. B.: Herpetic Fever with Stomatitis: Report and Discussion of a Case in Which the Virus Was Isolated, South. M. J. **25**:228-233 (March) 1932.

31. Long, P. H.: Herpetic Pharyngitis and Stomatitis: Report of Three Cases, J. Clin. Investigation **12**:1119-1125 (Nov.) 1933.

32. Burnett, F. M., and Williams, S. W.: Herpes Simplex: New Point of View, M. J. Australia **1**:637-642 (April 29) 1939.

33. Black, W. C.: Etiology of Acute Infectious Gingivostomatitis (Vincent's Stomatitis), J. Pediat. **20**:145-160 (Feb.) 1942.

34. Dodd, K.; Johnston, L. M. and Buddingh, G. J.: Herpetic Stomatitis, J. Pediat. **12**:95-102 (Jan.) 1938.

35. Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis: Etiology, Epidemiology and Clinical Picture of Common Disorder Caused by Virus of Herpes Simplex, J. A. M. A. **117**:999-1005 (Sept. 20) 1941.

rising protective antibody titers in their patients. Black fulfilled the postulates of Koch by inoculating the isolated virus into the mucous membrane of infants and thereby reproducing the disease. The various authors agreed on the term infectious or herpetic gingivostomatitis for the condition as revealed in their cases but varied somewhat in the description of their clinical observations. Some disagreement is recorded as to the identity of aphthous stomatitis, catarrhal stomatitis and membranous stomatitis with Vincent's stomatitis, fusospirochetal gingivitis, trench mouth and ulceromembranous stomatitis. However, Scott and Steigman sensibly commented that thirty descriptive terms are used to classify the various stages of herpetic stomatitis. This is an acute systemic infection characterized by fever, irritability, soreness of mouth, red swollen gums, oral fetor and regional lymphadenopathy. The primary finding is a tiny vesicle, which ruptures, leaving a shallow, round ulcer (aphthous ulcer) sometimes covered by a membrane. It may merge with adjacent ulcers. These lesions are most frequently found on the buccal and lingual surfaces but may also be present on the gums or anywhere else in the mouth or pharynx. The gums usually become red and swollen and bleed easily, and marginal ulcerations may develop. In a small percentage of the cases herpes simplex precedes or is associated with the oral changes. The disease is acute and self limited, and it usually runs its course in six to sixteen days. The various authors, in passing, relegated the fusospirochetes to the ash can of etiologic oblivion, where they probably belong. Scott and Steigman pointed out that trench mouth or Vincent's stomatitis in adults is due for an urgently needed reinvestigation in the light of the aforementioned observations.

A few instances of the disease in adults have been reported by Youmans and by Long. The latter isolated the herpes virus in 2 out of his 3 cases by repeated inoculation of animals. Thus the way has been paved to eliminate the term Vincent's disease entirely from any discussion of stomatitis.

Further to be differentiated is a new disease in infants and young children described by Buddingh and Dodd in 1944.[36] At the onset the mouth is sore and the mucous membrane of the lip, anterior margin and under surface of the tongue and the gums become fiery red and covered with tiny vesicles. These changes are followed by desquamation, leaving raw surfaces, which bleed easily. In older children with teeth, the involvement of the gums is severer, with swelling, vesicles and shallow ulceration. Many infants suffer from mild diarrhea. There is no fever, and the course is from three to ten days. Relapses may occur during the next two months. Contagion is striking, 16 instances having

36. Buddingh, J. G., and Dodd, K.: Stomatitis and Diarrhea of Infants Caused by Hitherto Unrecognized Virus, J. Pediat. **25**:105 (Aug.) 1944.

occurred among 30 infants in a nursery within a period of two weeks. Swabs from infected mouths readily produced keratitis through multiple passages in rabbits, differing from the inclusion body type due to the herpes virus. This virus was also found in nurses and an intern who remained free from any symptoms. One of the authors accidentally flicked some infected corneal filtrate into his mouth, and on the third day typical oral lesions developed. Further work showed that humoral protective antibodies developed and that there were no cross relationships with the herpes virus, and the feeding experiments in rabbits produced shallow ulcerations in the small intestine.

TREATMENT

There is little that can be said on the subject of therapy. The local lesions cannot be significantly influenced. Nothing stronger than solution of boric acid was used in the eyes. Some of the earlier authors felt that vigorous measures were needed to prevent serious ocular complications. Perhaps because the disease was milder such was not the case here. In the mouth, irrigations with potassium permanganate in a 1 : 4,000 dilution were as effective as anything else in the maintenance of cleanliness. It is felt that the use of caustic agents such as silver nitrate has no place in the treatment of diffuse lesions. Local anesthetics such as tetracaine hydrochloride or ethyl aminobenzoate, best used in a jelly, are of some slight value in relieving the soreness. As far as systemic therapy is concerned, penicillin in large doses was tried in case 19, without appreciable effect. The sulfonamide drugs were avoided because of the eruptive manifestations and the absence of any good or urgent indication for their use. High vitamin therapy was ineffectual when tried.

SUMMARY

1. Twenty cases have been reported of an obscure and little-recognized syndrome in young men, constituting an acute, probably infectious, self limited, febrile disease. Prodromal symptoms in the respiratory tract are followed by lesions of the skin and mucous membrane of the mucocutaneous junctions, characterized by vesicles and pseudomembranes and accompanied frequently with fever and occasionally with bronchopneumonia.

2. Three groups are recognized, based on severity and distribution of lesions. The first group, originally described by Hebra as erythema multiforme exudativum, includes mild conditions primarily involving the skin, with only slight involvement of the mucous membrane. The second group, described by Stevens and Johnson, includes extremely severe conditions, with extensive lesions of the mucous membrane, corneal scarring, panophthalmitis and blindness. The third group, including conditions of intermediate severity, is exemplified by the cases in the series described here.

3. The pathogenesis is obscure. Bacteriologic findings are not of significance. There is no evidence that ingestion of drugs is a factor. Because of the prodromes in the respiratory tract and generalized manifestations, it is felt that this is an air-borne, systemic disease probably due to a virus.

4. Experimental studies failed to demonstrate a humoral antibody response to the herpes simplex or elementary virus of the body type. Various experiments in inoculation with filtered saliva from 1 patient were largely noncontributory, although some suggestive lesions were produced in chick embryos. It is believed that future investigation directed along these lines is indicated, with the consideration of the use of human volunteers.

5. In the foregoing paragraphs the terms erythema exudativum multiforme, eruptive fever and Stevens-Johnson disease have been used interchangeably in the description of the syndrome under discussion. The various names proposed and used are ponderous, frightening and misleading in that they direct attention almost exclusively to the skin. Erythema exudativum multiforme means little in the majority of cases in this series, in which dermatologic lesions did not occur. The term "erythema pluriorificialis exudativum" is better chosen in that it refers also to the orifices of the body, but it is still too long and cumbersome for common usage and has descriptive meaning only. Until the causative agent is found, appropriate naming of this disease will not be possible.

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CIRRHOSIS OF THE LIVER WITH MASSIVE HYDROTHORAX

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ALTHOUGH the first description of massive hydrothorax occurring in a case of cirrhosis of the liver has been attributed to Laennec, it has since received scant clinical attention. As a result, its development frequently transforms an otherwise obvious case of cirrhosis of the liver into a puzzling diagnostic problem. It has been cited by Vedel and Puech [1] as occurring in 8 to 9 per cent of all cases of cirrhosis of the liver. However, these authors arrived at this relatively high incidence by the inclusion of cirrhotic patients having tuberculous or cardiac pleural effusions. Few reports are available in which the complicating causes for hydrothorax have all been demonstrated to be absent.

Goffart [2] and Benedetti [3] each reported a small series of cases of cirrhosis with hydrothorax and attempted to exclude the more usual causes of hydrothorax. Christian [4] reported a case of hydrothorax on the left side requiring nine thoracenteses, with the withdrawal of a total of 13,100 cc. of fluid. An additional case of cirrhosis, in which the diagnosis was confirmed by biopsy, without any clinically demonstrable pathologic changes in the lungs, mediastinum, pleura or heart was reported by Frothingham.[5] The recurrent hydrothorax involving the right side necessitated two hundred and eleven thoracenteses for the removal of a total of 467,100 cc. of fluid from the right pleural cavity. In view of this paucity of reported cases, it seems reasonable to conclude that massive hydrothorax with no etiologic basis other than

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1. Vedel, S. N., and Puech, A.: Considerations sur les épanchements pleuraux au cours de la cirrhose de Laënnec, Bull. Soc. d. sc. méd. et biol. de Montpellier **8**:120, 1927.

2. Goffart, M.: Étude clinique et biologique des épanchements pleuraux des cirrhotiques, Rev. belge sc. méd. **10**:341, 1938.

3. Benedetti, P.: Ill grande idiotorace destro nel corso della cirrosi epatica, Arch. di pat. e clin. med. **20**:119, 1939.

4. Christian, H. A.: Bloody Pleural Fluid, an Unusual Complication of Cirrhosis of the Liver, Ann. Int. Med. **10**:1621, 1937.

5. Frothingham, J. R.: Cirrhosis of the Liver Complicated by Persistent Right Hydrothorax and Ascites, New England J. Med. **226**:679, 1942.

cirrhosis of the liver is rare. During the years 1930 to 1945 only 6 cases of this syndrome were seen at this laboratory. These cases were selected from approximately 600 cases of cirrhosis of the liver. We have observed, as have the older authors, that not infrequently small amounts of pleural effusion are found in cases of cirrhosis of the liver, but these are usually the result of associated pathologic conditions and not of the hepatic disease. For this reason we have established the following criteria for the selection of our cases: (1) the presence of an uninfected hydrothorax of more than 500 cc. possessing the characteristics of a transudate and (2) the presence of cirrhosis of the liver uncomplicated by any other disease which may produce hydrothorax.

Because of the high incidence of cardiorenal disease in this age group and because of the relationship of disease of the heart, lungs and kidneys to the accumulation of pleural fluid, a special effort was made to exclude patients having significant pathologic changes in these organs. To this end all patients with hearts weighing more than 350 Gm. or showing gross or microscopic evidence of organic cardiac disease were excluded. To exclude cardiac failure further, patients with lungs weighing more than 450 Gm. or showing gross or microscopic evidence of significant pulmonary edema were omitted from the series. In all cases the kidneys were within normal limits grossly and microscopically.

Of the 6 cases included in the present series, 2 have been selected for citation in detail.

Case 1.—A 65 year old ship rigger entered the hospital complaining of progressive weakness and dyspnea of about three months' duration. He had lost 15 pounds (6.8 Kg.) during this period and had noted the onset of a cough producive of whitish sputum. His appetite had been poor for several months prior to his admission to the hospital. Until a year before admission he had consumed large quantities of alcoholic beverages. His previous health had been good except for an attack of typhoid fever in 1906.

The blood pressure was 125 systolic and 80 diastolic. He appeared acutely ill and was decidedly orthopneic. The skin of the face and upper part of the thorax was ruddy, and a number of telangiectases were present. No jaundice was noted. The trachea was deviated to the left, and the entire right side of the chest was flat to percussion, with absence of breath sounds and diminished fremitus A smooth, nontender edge of liver was palpated at the level of the umbilicus.

The urine was normal except for the presence of bile. The hemoglobin content was 14 Gm. per hundred cubic centimeters. The white blood cell count was 9,650. The prothrombin time was 55 per cent of normal. The total serum protein content varied between 5.93 and 6.99 Gm. per hundred cubic centimeters. The nonprotein nitrogen content was 27 mg. per hundred cubic centimeters. The acid phosphatase content was 1.32 units per hundred cubic centimeters and the alkaline phosphatase level 1.51 units. The cephalin flocculation test gave a reaction of 3 plus, and the hippuric acid excretion was 0.88 Gm. Inoculation of gastric washings into a guinea pig showed them to be negative for tuberculosis.

From 1,000 to 4,000 cc. of clear yellow to cloudy fluid was removed from the right pleural cavity on numerous occasions at intervals varying from three days to three weeks. The specific gravity of this fluid varied between 1.013 and 1.016. Culture and inoculations of a guinea pig with it showed it to be sterile. Repeated histologic sections of the sediment were reported negative for tumor cells except for one specimen reported as "suggestive of carcinoma."

Roentgenograms of the chest showed a massive accumulation of fluid on the right, with atelectasis and displacement of the mediastinum to the left. A series of roentgenograms of the gastrointestinal tract and a series of the bony skeleton were noncontributory. The electrocardiogram was within normal limits. Peritoneoscopy did not demonstrate conclusively the presence of cirrhosis, because of poor visualization of the liver. Bronchoscopy revealed only tracheobronchial displacement, with mucosal scarring suggestive of healed tuberculosis.

The patient remained in the ward for four months while these diagnostic studies were performed. He required repeated thoracentesis because of the rapid reaccumulation of the fluid in the right pleural cavity. He became progressively weaker, was disoriented during the last two weeks of his stay in the hospital and died in a stuporous condition. The diagnosis on discharge was bronchiogenic carcinoma with metastases to the pleura, recurrent massive hydrothorax on the right side, alcoholic cirrhosis of the liver and malnutrition.

An autopsy was performed thirty-two hours after death. Only the pertinent findings are given.

The peritoneal cavity contained approximately 500 cc. of clear, straw-colored fluid. The right pleura was thickened to 0.4 cm. The right pleural cavity contained 3,000 cc. of clear, yellow fluid. Several bandlike adhesions bound the apex of the collapsed right lung to the thoracic wall. The left pleural cavity was moist but contained no free fluid. The mediastinum was deviated to the left. The pericardial cavity contained an estimated 50 cc. of straw-colored fluid. Grossly, the diaphragm was intact.

The right lung weighed 220 Gm. and the left 420 Gm. The right lung was small, collapsed and covered by a thick layer of stringy yellow fibrin. The cut surface was firm, red and meaty. The left lung appeared slightly congested, and a foamy fluid emerged from the bronchioles on compression of the lung. The vessels, trachea and bronchi were not remarkable. The hilar and mediastinal lymph nodes were not enlarged.

The liver weighed 910 Gm. The capsular surface was tawny and finely nodular, the nodules measuring 0.1 to 0.3 cm. in diameter. At the anterior margin of the left lobe was a depresseed, soft, red area, 2 cm. in diameter, which extended into the hepatic substance for a distance of 1 cm. The liver was firm and resistant to section, and the cut surface showed thin, gray septums dividing it into nodules similar to those seen on the surface. The heart, kidneys and brain were grossly within normal limits.

Microscopic examination of the various tissues substantiated the anatomic findings. The pleura of the right lung was thickened, vascularized and covered by a layer of fibrin. The alveoli were decidedly compressed and contained no inflammatory reaction. The left lung showed only moderate congestion of the blood vessels. The lobular architecture of the liver was destroyed by broad bands of fibrous tissue, for the most part portal in distribution but occasionally bisecting lobules. The connective tissue contained numerous small bile ducts, lymphocytes, an occasional polymorphonuclear leukocyte and scattered small nests of hepatic cells. The normal central relationship of the veins was lost. Scattered focal areas of bile stasis were present. Only a few hepatic cells were vacuolated,

and alcoholic hyalin could not be demonstrated. A section taken from the anterior edge of the left lobe of the liver showed a partially fibrosed cavernous hemangioma.

The anatomic diagnosis was cirrhosis of the liver, unclassified type, with ascites, massive hydrothorax involving the right side and atelectasis of the right lung.

Comment.—The clinical course in this case was dominated by a massive hydrothorax which rapidly reaccumulated after thoracentesis. The cause of this hydrothorax remained undetermined in spite of diagnostic studies. A diagnosis of cirrhosis of the liver was established, but no relationship between the two conditions was considered. At necropsy cirrhosis of the liver, unclassified type, with massive hydrothorax on the right side and atelectasis of the right lung, was found.

CASE 2.—A 24 year old woman entered the hospital for the first time, complaining of pleuritic pain on the right side of eleven days' duration. The right side of her chest had been strapped by her local physician. Three months previously she had given birth to a living child, her pregnancy being complicated by toxemia in the eighth month. No jaundice, loss of weight or loss of appetite had been noted at any time.

The temperature was 96.6 F., the pulse rate 71 and the respiratory rate 20. The blood pressure was 98 systolic and 78 diastolic. There was limited motion of the right side of the chest, with decreased resonance to percussion and suppression of the breath sounds. A soft blowing apical systolic murmur was heard.

An uncatheterized specimen of urine contained albumin (4 plus) and was loaded with red cells. The hemoglobin content was 11 Gm. per hundred cubic centimeters. The white blood cell count was 7,650. The serum nonprotein nitrogen content was 29 mg. per hundred cubic centimeters. A phenolsulfonphthalein test resulted in the excretion of 100 per cent of the dye in one hour. The Aschheim-Zondek test elicited a negative reaction. The reaction to a tuberculin patch test was strongly positive. Culture of the pleural fluid was sterile, and on inoculations of a guinea pig samples of pleural fluid, gastric washings and sputum were shown to be negative for tuberculosis.

A thoracentesis was performed, and 800 cc. of clear yellow fluid was withdrawn from the right pleural cavity. After ten days in the ward the patient was discharged for rest in bed at home to await the reports on the inoculation of a guinea pig. The diagnosis on discharge was pleurisy with effusion and questionable tuberculosis.

Second Admission (Ten Weeks Later).—Six weeks after the patient's discharge a second thoracentesis had been performed and 1,000 cc. of clear, yellow fluid had been withdrawn from the right pleural cavity. Two weeks later the patient noticed that toward the end of the day her feet were swollen. A week later an itching eruption over the lower part of the legs appeared, and this spread to the thighs, abdomen and upper arms. On the day before her admission she experienced a pain in the right infraclavicular region, which was aggravated by coughing or deep breathing and partially relieved by lying on the right side.

Physical examination at this time showed an erythematous, punctate, partially confluent, scaling rash over the skin of the tibial regions, abdomen and upper part of the arms. The trachea was deviated to the left, and there was limited motion of the right side of the thorax, with flatness and absence of breath sounds up to the level of the scapular angle. The heart was displaced to the left. The abdomen was protuberant, with shifting dulness and a fluid wave. The liver and

spleen were palpable 2 fingerbreadths below the costal margins. Mild edema of the legs and thighs was noted.

The total protein content was 4.51 Gm. per hundred cubic centimeters. The cephalin flocculation test gave a reaction of 4 plus and the prothrombin time was 35 per cent of normal. A hippuric acid test showed the excretion of 0.3 Gm. in one hour. The urine revealed bile (1 to 2 plus) occasionally, and the stool was light tan to brown and reacted negatively to the guaiac test.

On thoracentesis a straw-colored fluid with a specific gravity of 1.004, 749 red cells and 18 white cells per cubic millimeter was withdrawn. A histologic section of the sediment was reported as showing "atypical cells suggestive of but not typical of carcinoma." Cultures of the fluid and repeated cultures of the blood were sterile.

Roentgenologic examination of the chest on three occasions disclosed large amounts of fluid in the right pleural cavity. An electrocardiogram was interpreted as suggestive of myocardial involvement.

During the ensuing six weeks the patient gave increasing evidence of severe hepatic failure, with the development of massive ascites and edema, jaundice, low grade fever, lethargy and finally coma. A total of 5,785 cc. of fluid was obtained on three thoracenteses, and one abdominal paracentesis yielded 2,600 cc. of fluid during the six weeks' course. She was placed on a high vitamin, high protein, high carbohydrate and low fat diet. Her rapid downhill course persisted, and she died in spite of supportive therapy six weeks after her final admission and sixteen weeks after her initial entry to the hospital.

The diagnosis on discharge was hepatic failure, subacute yellow atrophy (?), cirrhosis of the liver with superimposed hepatoma (?), lupus erythematosis (?) and Hodgkin's disease (?).

An autopsy was performed eighteen hours after death. Only the pertinent findings are discussed.

The peritoneal cavity contained about 700 cc. of blood-tinged fluid. The right pleural space contained 2,500 cc. of clear straw-colored fluid, and the right lung was decidedly collapsed. Several thin, weblike adhesions were present posteriorly. The left pleural cavity contained about 800 cc. of similar straw-colored fluid. The pericardial cavity contained approximately 60 cc. of clear fluid. The diaphragm was intact grossly.

The right lung weighed 300 Gm. and the left 420 Gm. The right lung was small, firm and gray. The cut surface was gray and dry. The left lung showed a moist, red, subcrepitant surface on cut section.

The liver weighed 1,020 Gm. The surface was irregularly nodular and had a dull yellow color. The liver sectioned easily and was flabby, and the cut surface showed a similar yellow nodularity with intervening gray strands of fibrous tissue. Small, red areas of softening were scattered over the cut surface.

The heart, kidneys and brain revealed no abnormalities. Microscopic examination of sections from the various organs substantiated the gross anatomic findings.

The lungs showed congestion of the vessels and collapse of the alveoli. No inflammatory exudate was present. The liver showed widespread destruction of hepatic cells, with collapse of the stroma and replacement by loose connective tissue containing large numbers of small bile ducts and congested sinusoids. In several areas the remaining hepatic cells appeared necrotic and were surrounded by polymorphonuclear leukocytes and vacuolated phagocytes. Several large nodules of regenerating hepatic cells surrounded by a band of compressed fibrous tissue were observed.

The anatomic diagnoses were healed acute yellow atrophy with superimposed acute yellow atrophy, ascites, bilateral hydrothorax, atelectasis of the right lung and pulmonary congestion.

Comment.—The initial finding in this case of a recurrent hydrothorax attributed to tuberculosis was followed ten weeks later by signs suggestive of hepatic failure. Although a relationship between the hydrothorax and the hepatic disease was considered, this diagnosis was not accepted. As a result, no definite diagnosis was established clinically. At autopsy an acute yellow atrophy superimposed on a healed acute yellow atrophy with bilateral hydrothorax and ascites was found.

Summary of Six Cases of Cirrhosis of the Liver with Massive Hydrothorax

Case; Sex; Age, Yr.	Amount (Cc.) and Character of the Pleural Fluid		Duration of Hydrothorax	Ascites (Cc.) (Amount and Character of the Fluid)	Anatomic Type of Cirrhosis	Clinical Diagnosis
	Right Side	Left Side				
1 M 65	3,000, clear yellow	0	6 mo.	500, clear yellow	Unclassified	Bronchiogenic carcinoma with pleural metastases and massive recurrent hydrothorax on the right and alcoholic cirrhosis
2 F 24	2,500, straw colored	800, straw colored	3½ mo.	700, blood tinged	Healed acute yellow atrophy with superimposed acute yellow atrophy	Right pleural effusion; tuberculosis (?); hepatic failure; subacute yellow atrophy (?); cirrhosis with hepatoma (?); lupus erythematosus (?); Hodgkin's disease
3 M 60	2,000, straw colored and fibrinous	1,000, straw colored and fibrinous	6 mo.	1,000, straw colored	Alcoholic	Alcoholic cirrhosis with bleeding; esophageal varices
4 M 42	1,000, bile tinged	200, bile tinged	1 mo.	4,700, bile tinged	Alcoholic	Alcoholic cirrhosis
5 F 33	0	800, clear yellow	2 wk.	3,000, clear yellow	Alcoholic	Cirrhosis; hydrothorax on the left; ascites
6 F 44	0	900, straw colored	2 wk.	3,000, clear yellow	Alcoholic	Cirrhosis; ascites; bilateral hydrothorax

The remaining 4 cases, as well as the preceding 2, are summarized in the accompanying table.

COMMENT

Analysis of these cases shows certain features worthy of comment. The ages of the patients ranged from 24 to 65 years. That one half of these patients were in the younger age group is explained by the fact that the criteria used for selection of cases tended to eliminate patients in the older age group. The cases were equally divided between men and women.

The pleural effusions frequently were impressive in amount, the total volumes ranging from 800 to 17,250 cc. The fluid was found in one instance in the right pleural cavity alone, in two instances only in the left and in three instances bilaterally. In terms of total volume

it was predominantly right sided in distribution. It had the characteristics of a transudate, with a specific gravity below 1.018 and a total protein content below 4 per cent. In the various protocols the fluids were described as clear yellow and straw colored, and once it was described as bile stained. As in Christian's case,[4] sanguineous fluid was found clinically only after repeated thoracenteses had been performed, the color having changed from a clear yellow to blood tinged. Fibrin strands were found occasionally. The known duration of the hydrothorax in all these cases was sufficiently long—from two weeks to months—to exclude the possibility of the fluid's having collected only during the agonal period.

Ascitic fluid was found at autopsy in all these cases, but in three instances it was much less in amount than the associated pleural collection. It is notable that the ascites usually elicited considerable clinical interest, whereas the larger pleural effusions frequently were ignored. As might be expected, moderate to excessive edema of the lower extremities occurred in the patients with massive acites. In none of the cases was there a significant degree of hydropericardium.

No conclusion can be drawn concerning the type of cirrhosis which is associated with hydrothorax. In 4 of our cases it was of the alcoholic type, in 1 it was acute yellow atrophy and in 1 it was of the unclassified type. No cases of biliary or pigmentary cirrhosis fulfilled the criteria for this series.

The explanation of the occurrence of the pleural fluid in cases of cirrhosis of the liver remains obscure. However, since all other causes for hydrothorax have been ruled out, we must attribute some causal relationship between the cirrhosis of the liver and the pleural fluid. In recent years Meigs [6] has called attention to the association of hydrothorax and ascites with certain large ovarian tumors. The theory has been advanced that fluid may pass from the abdominal cavity to the pleural cavity by way of the lymphatic vessels of the diaphragm. In substantiation of this hypothesis Meigs injected india ink into the peritoneal cavity and demonstrated its passage into the pleural cavity. India ink injected into the pleural cavity failed to appear in the peritoneal cavity. Additional support for this theory was found in the similarity of the fluid in the pleural and peritoneal cavities in certain cases, both fluids having similar protein content and electrophoretic distribution.

Benedetti,[3] while acknowledging the possibility of transdiaphragmatic passage of fluid, preferred in cases of cirrhosis to attribute the accumulation of pleural fluid to the increase in venous pressure in the azygos veins subsequent to the formation of collateral anastomoses between the portal and azygos systems.

One factor which has been difficult to evaluate is the relationship of hypoproteinemia and hypoalbuminemia to the production of massive

6. Meigs, J. V.; Armstrong, S. H., and Hamilton, H. H.: A Further Contribution to the Syndrome of Fibroma of the Ovary with Fluid in the Abdomen and Chest (Meigs' Syndrome), Am. J. Obst. & Gynec. **46**:19, 1943.

hydrothorax. While hypoproteinemia is frequently associated with cirrhosis of the liver, the relationship of hypoproteinemia to the production of hydrothorax is not so clearly defined. Goffart [2] stated that in his experience hypoproteinemia exerts no constant or major influence on the production of hydrothorax. In all our cases in which the determination was made, the level of the serum albumin was low. However, similar cases of cirrhosis with low albumin and total protein levels are found frequently without a significant degree of hydrothorax. Hence, hypoproteinemia and/or hypoalbuminemia may reasonably be excluded as the primary etiologic factor in the production of hydrothorax associated with cirrhosis.

Because the occurrence of hydrothorax during the course of cirrhosis is not common, a perplexing clinical problem may arise when these two conditions are associated. The first case is typical of some of the problems. Throughout the patient's stay in the hospital the presence of rapidly recurring massive hydrothorax dominated the clinical course of the disease, and the cirrhosis was regarded as an incidental finding. Cardiac failure, tuberculosis, intra-abdominal malignant tumor and tumor metastatic to bone were excluded by appropriate studies. An intensive study, including repeated roentgenograms, bronchoscopy and numerous histologic sections of sediment of pleural fluid, was made in an attempt to detect a suspected bronchiogenic carcinoma. In spite of the noncontributory results of the diagnostic procedures, the final clinical diagnosis was held to be bronchiogenic carcinoma with pleural metastases to account for the hydrothorax.

The second cited case presented an equally difficult diagnostic problem, since cirrhosis was not evident and the presenting signs and symptoms were those of a recurring hydrothorax. Roentgenograms of the chest revealed no evidence of underlying pulmonary tuberculosis. The diagnosis at this time was pleural effusion of tuberculous origin, and the patient was given rest in bed pending a report of inoculations of a guinea pig with sputum, gastric washings and pleural fluid. Ten weeks later the clinical picture had become more complex, with the onset of the signs and symptoms of acute hepatic failure. At this time less common diagnoses such as lupus erythematosus disseminatus, Hodgkin's disease, Pick's disease and hepatoma superimposed on cirrhosis of the liver were considered but not established. The case came to autopsy with the diagnosis of pleural effusion and hepatic failure, both of undetermined origin. The clinical confusion caused by this combination of symptoms is shown not only by the variety of diagnoses considered but also by the statement in the clinical record that "the appearance of massive pleural effusion before the appearance of ascites is puzzling if the entire clinical course is to be explained on the basis of damage to the liver." It is interesting also that the hydrothorax occurred ten weeks before the hepatic failure became evident. Pathologically there was an old cirrhotic process present in the liver as well as a superimposed acute necrosis.

It is noteworthy that in Christian's case [4] diagnostic difficulties were encountered also. As he said,

> The diagnosis in this case, particularly after the development of the hemorrhagic fluid in the left pleural cavity with its rapid reaccumulation, was actively discussed by the staff. At first the diagnosis of cirrhosis of the liver was held. With pulmonary and pleural signs appearing, it was thought that these resulted from a complicating inflammation. When the pleural fluid was found bloody and reaccumulated so rapidly, diagnosis veered to neoplasm, presumably primary in liver, as none could be demonstrated elsewhere (negative roentgen-ray study of gastrointestinal tract; no evidence of prostatic tumor).

This discussion does not imply that an etiologic factor in hydrothorax other than cirrhosis of the liver should not be carefully searched for in these cases. Rather it is to be emphasized that when all other possible causes for the hydrothorax have been excluded the pleural fluid may reasonably be considered to be associated with the cirrhosis.

CONCLUSION

Massive hydrothorax with no etiologic basis other than cirrhosis of the liver is rare. Six cases are presented, 2 in detail. The precise mechanism of the accumulation of pleural fluid in cases of cirrhosis remains obscure. When these two conditions are associated, perplexing diagnostic problems arise. When the appropriate studies rule out other causes of massive hydrothorax, the pleural fluid may reasonably be considered to be associated with cirrhosis of the liver.

STEVENS-JOHNSON SYNDROME

Report of Nine Patients Treated with Sulfonamide Drugs or Penicillin

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STEVENS and Johnson [1] in 1922 described a "new" eruptive fever associated with stomatitis, ophthalmia, cutaneous eruption and constitutional symptoms. This syndrome is usually considered uncommon; we have seen but 15 patients with it out of 115,000 patients admitted to the hospital since September 1942, 6 of whom had only simple catarrhal conjunctivitis and are not included in this report. This syndrome deserves more emphasis because tragic complications of the eyes, consisting of corneal ulceration or panophthalmitis with partial or complete loss of vision, have been frequent in reported cases. Since these severe complications of the eyes did not occur in our 9 patients treated with sulfonamide drugs and/or penicillin, we feel that their cases should be reported.

Stevens-Johnson syndrome has been referred to as erythema multiforme bullosum with involvement of the mucous membranes of the eyes and mouth,[2] erythema exudativum multiforme with opthalmia and stomatitis [3] or severe erythema multiforme.[4]

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1. Stevens, A. M., and Johnson, F. C.: New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:526 (Dec.) 1922.

2. Ageloff, H.: Erythema Multiforme Bullosum with Involvement of Mucous Membranes of Eyes and Mouth (Stevens-Johnson's Disease): Report of a Case, New England J. Med. **223**:217 (Aug. 8) 1940.

3. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report on Two cases in Children with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. **12**:151 (Feb.) 1938.

4. Lever, W. F.: Severe Erythema Multiforme: Report of Two Cases of the Type Ectodermosis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One case, Arch. Dermat. & Syph. **49**:47 (Jan.) 1944.

Bailey [5] expressed the belief that this syndrome was a form of erythema multiforme with severe lesions of the eyes. He reported 3 patients who had some loss of vision. Ginandes [6] in 1935 reviewed 9 cases. Seven of the patients became totally blind, and the remaining 2 showed some impairment of vision. Lever [4] in 1944 gave an excellent bibliography and summary of the clinical manifestations of this syndrome and reported 2 cases. Conjunctivitis persisted in both cases, with development of conjunctival scarring and corneal opacities in 1.

The causation of this syndrome is unknown. Many factors have been suggested as playing a part; various micro-organisms and drugs having been blamed, including the sulfonamide drugs. Hemolytic Staphylococcus aureus and Vincent's organisms have been among the most commonly blamed bacteria. In our series, both organisms have been found, but it is our opinion that these are secondary invaders.

The syndrome consists in an acute illness accompanied with the appearance of vesicular, bullous and ulcerative lesions on the mucous membranes, most characteristically those of the eyes, nose, mouth, tracheobronchial tree, esophagus, anus and genitalia. Lesions of the skin may or may not be present, being either erythematopapular or vesiculobullous in nature, but when present are of the type seen in an ordinary case of erythema multiforme. The patients may be seriously ill, or they may have few systemic symptoms. Fever may or may not be present, and the degree of elevation of the temperature varies considerably. Recurrences have been frequent, and generally the later attacks are less severe than the initial one. Most of the patients are in the younger age group.

The symptomatology is protean. Almost all the mucous membranes have been reported to be the site of appearance of the lesions. Conjunctivitis, rhinitis, stomatitis, pharyngitis, tracheobronchitis, urethritis, balanitis, hematuria, generalized lymphadenopathy and splenomegaly and lesions of the anal mucosa have been reported.

With such a multiplicity of sites involved, the possibilities of complications are great. The most dramatic complications in the patients who survive are to be found in the eyes, where decided purulent conjunctivitis leads at times to the development of perforation of the cornea and the appearance of panophthalmitis, with total loss of vision, or to corneal scarring with diminution of the visual acuity or chronic conjunctivitis and the formation of symblepharon, with subsequent distor-

5. Bailey, J. H.: Lesions of Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, Arch. Ophth **6**:362 (Sept.) 1931.

6. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson Syndrome), Am. J. Dis. Child. **49**:1148 (May) 1935.

tion of the eyelids. Therefore, early diagnosis and institution of proper treatment to attempt to prevent permanent ocular involvement are imperative.

In consideration of the differential diagnosis, the most important conditions to be ruled out, as Lever indicated, are foot and mouth disease, Vincent's angina, drug eruptions, pemphigus, venereal penile lesions and urethritis.

Drug eruptions may be difficult to distinguish. The lesions may be identical in appearance, but the history, the notable systemic involvement and the course should aid in the clarification. In consideration of drug eruptions, it is of interest that the sulfonamide drugs have been implicated as precipitating factors or specific causes in some cases of erythema multiforme bullosum. The patient in case 7 had been given sulfadiazine several weeks prior to the onset of the Stevens-Johnson syndrome. He had experienced three previous attacks, prior to none of which had he received any sulfonamide drugs. The use of the sulfonamide compounds in our cases did not appear to aggravate the lesions but rather had the directly opposite effect.

The appearance of foot and mouth disease is clinically similar to that of the Stevens-Johnson syndrome. The differentiation depends on the inoculation of laboratory animals when foot and mouth disease is suspected, according to Klauder.[7]

Vincent's angina does not cause the large bullous lesions on the mucous membranes so characteristic of the Stevens-Johnson syndrome (fig. 3 *A*).

Pemphigus vulgaris has an entirely different onset and course than erythema multiforme bullosum.

Penile lesions require a dark field examination and serologic analysis of the blood, which revealed normality in our cases. The appearance of the rash on the skin, and the bullous involvement of other mucous membranes should establish the differential diagnosis.

Urethritis may be suspected in patients complaining of urinary symptoms but should offer no difficulty in the decision as to whether it is or is not a part of the general picture.

As a general rule, the prognosis in cases of Stevens-Johnson syndrome is favorable as regards life, only 4 fatal cases having been reported in the world's literature, according to Lever.

Until recently, treatment has consisted in supportive and symptomatic measures. Five cases have been reported in which either sulfonamide drugs or penicillin were employed in the treatment of the patients, 4 of

7. Klauder, J. V.: Ectodermósis Erosiva Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exudativum Multiforme, Arch. Dermat. & Syph. **36**:1067 (Nov.) 1937.

whom made complete recoveries. Givner [8] reported 2 cases of this syndrome, in both of which one of the sulfonamide drugs had been given therapeutically, and in both cases complete recovery ensued. He added a third case of a patient under treatment at the time his paper was being written. Erger [9] reported 1 case of a patient treated with sulfadiazine in whom corneal scarring developed, and Kove [10] reported the cases of 2 patients, both of whom made complete recovery, both of whom received sulfadiazine and 1 of whom had penicillin instilled in the eye in addition. To these we are adding reports of 9 cases of patients treated with either sulfonamide compounds or penicillin, 8 of whom made complete recovery. In the other patient chronic conjunctivitis and mild symblepharon developed but without evidence of corneal scarring.

REPORT OF CASES

CASE 1.—The patient was admitted to the hospital on Sept. 20, 1942, with a complaint of fever, headache, malaise and a nonproductive cough starting three days prior to admission and becoming progressively worse. He appeared moderately ill. There was a mucopurulent nasal discharge, slight scleral injection and mild cervical adenitis. The white blood cell count was 4,550, with 66 per cent polymorphonuclear cells. Urinalysis yielded normal results. A diagnosis of influenza was made. Five days later he was extremely ill, the temperature was 104 F., he was coughing considerably, the pharynx was inflamed and a single bulla was noted in the mouth and one on the skin. By the next morning there were present erosive stomatitis and pharyngitis, with some erythematous vesicles on the hands. He was given a blood transfusion and fluids intravenously. Bilateral severe purulent conjunctivitis rapidly developed, and his temperature remained near 104 F. Because of the seriousness of the illness, sulfadiazine therapy, consisting of administration of 4 Gm. initially and 1 Gm. every four hours, was started. Additional transfusions were given. Cultures of material taken from the mouth and eyes showed hemolytic Staph. aureus. Cultures of the blood were sterile. A roentgenogram of the chest showed increased pulmonary markings but no infiltration. Gradual improvement followed, with the eventual clearing of all the lesions except for mild persistent bilateral conjunctivitis, with no evidence of corneal opacities but with granulations of the lids and mild symblepharon. He was separated from the service eventually because of the chronic conjunctivitis and emotional instability.

CASE 2.—The patient, aged 25, was admitted to the hospital on Jan. 22, 1943, with a history of sore throat for one day. The tonsils presented a follicular exudate, and the temperature was 99.4 F. He was given sulfathiazole. Three days later large bullae developed in the mouth, and the following day there were conjunctivitis and papular and vesicular lesions on erythematous bases on the extremities. The

8. Givner, I., and Ageloff, H.: Stevens-Johnson Disease with Complete Visual Recovery, New York State J. Med. **41**:1762 (Sept. 1) 1941.

9. Erger, B. D.: Erythema Multiforme Pluriorificialis (Stevens-Johnson Disease), Mil. Surgeon **95**:308 (Oct.) 1944.

10. Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), Am. J. M. Sc. **210**:611 (Nov.) 1945.

white blood cell count was 11,600, with a polymorphonuclear content of 76 per cent. The urine was normal. A culture of material from the eyes showed Staphylococcus albus and Staph. aureus. On January 27, sulfadiazine was substituted for the sulfathiazole, and sulfathiazole ointment was ordered for the eyes. There was complete subsidence of all lesions except for the development of mild adhesions between the prepuce and glans penis.

CASE 3.—The patient, aged 18 years, was admitted to the hospital on Jan. 9, 1944, with the history of a sore throat for one week and a sore mouth and profuse discharge from the eyes for two days. He had had two previous similar attacks, in March and September 1943, the first being the worst. He appeared moderately ill. The temperature was 102.8 F. and the pulse rate 100. There were multiform erythematous lesions, chiefly papules and vesicles, on the palms, wrists and lower parts of both legs. There were a few vesicles on the lips, while the tongue, palate and buccal mucosa appeared gray and dull and displayed a few bullae. There was a profuse serofibrinous discharge bilaterally from the eyes, with definite chemosis and photophobia. The white blood cell count was 14,650, with a polymorphonuclear content of 83 per cent. The urine was normal, and smears were negative for Vincent's organisms but cultures of material from the throat were later reported to show beta hemolytic streptococcus and Streptococcus viridans. The sedimentation rate was 33 mm. in one hour. He was given sulfathiazole both orally and locally. After administration of a total of 12 Gm. of the drug his temperature was normal, and it remained so until he was discharged as cured on February 1.

CASE 4.—The patient, aged 22 years, was admitted to the hospital on Feb. 7, 1944, with a history of pain in the jaws, watering of the left eye and a penile sore for five days. He had experienced a similar attack the preceding year. The temperature was 99.6 F. and the pulse rate 100. There was an erosive stomatitis, conjunctivitis of the left eye and erosion of the glans penis. There were vesicles on erythematous bases on both hands. He was given sulfathiazole orally and sulfathiazole jelly for use in the eye. He was discharged as completely cured on Feb. 23, 1944.

CASE 5.—The patient, aged 28, was admitted to the hospital May 5, 1944 with a history of sore throat and mouth, with difficulty in swallowing, burning of the right eye and cough and fever for two days. He experienced a similar episode two years previously. The temperature was 99.6 F., there was mild bilateral conjunctivitis, the pharynx was inflamed and showed pronounced ulcerations and there was mild balanitis present. Cultures of material from the penis and eye showed a nonhemolytic Staph. aureus. The white blood cell count was 14,000, with a polymorphonuclear content of 76 per cent. The urine was normal. He was given sulfathiazole orally and sulfathiazole sesquihydrate drops in the eyes. There was a prompt subsidence of all lesions.

CASE 6.—The patient, aged 23, was admitted to the hospital on Jan. 29, 1945 with a history of difficulty in swallowing for three days. He was unable to eat solid food and could swallow liquids only with difficulty. He had noticed blisters on his arms and legs two days before his admission. Examination showed an acutely ill man, with a temperature of 102 F. and a pulse rate of 90. There were small bullae on erythematous bases scattered over the extremities, with a few on the neck, trunk, buttocks and penis and one at the anus. There were extensive ulcerations on the buccal mucosa, pharynx, tonsillar pillars, gums and lips, with fresh bullae on the pharynx. There was decided fetor oris. There was an erythematous area in the right eye at the outer canthus, but no ulcers were present.

A smear from the mouth showed Vincent's organisms, while culture of material from the penis showed Str. viridans. The zone of inhibition for the latter organism was only 24 mm. to 5.0 units of penicillin. Despite this, because of the severity of the clinical appearance, administration of penicillin by intramuscular injection was instituted. There was prompt response to therapy, and by February 6 the lesions were all healing. He was subsequently discharged as cured.

CASE 7.—The patient, aged 25, was admitted to the hospital on June 30, 1945. Two weeks previously he had received a course of sulfadiazine for four days. Three days before his present admission he noted a sore mouth, pain on swallowing, a penile sore and pain on urination. These became worse, and vesicles developed on his arms and legs. He had had three previous attacks similar in nature. He was mildly ill, with a temperature of 100.6 F. The skin showed vesicular lesions of erythema multiforme on the extremities and on the penis. There was considerable ulceration on the gums, pharynx and nasal mucosa. The white blood cell count was 17,300, with a polymorphonuclear content of 78 per cent. The urine contained 3 to 4 pus cells per high power field. Culture of material from the mouth showed hemolytic Staph. aureus, with a 22 mm. zone of inhibition with 0.5 units and 38 mm. with 5.0 units of penicillin. Culture of material from the penis showed Str. viridans. The following day there was chemosis at the outer canthus of the right eye, and he was given penicillin jelly, 5,000 units per cubic centimeter, in a water-soluble base, to use in the eye. During the course of the next three weeks the lesions all healed.

CASE 8.—The patient, aged 27 years, was admitted to the hospital on March 30, 1945, with a history of having noticed several small ulcers in the mouth and on the lips four days before, followed by small blisters on the glans penis. He had had two attacks of similar nature in the past, in both of which the eyes were involved. Examination showed a moderately ill man, with a temperature of 102 F. and a pulse rate of 108. There were ulcerations of the lips and oral mucosa and several discrete lesions of the iris type on the glans penis. Culture of material from the mouth showed beta hemolytic streptococcus and Str. viridans. The penicillin cup test showed only a 16 mm. zone of inhibition with 0.5 units. The white blood cell count was 9,500, with a polymorphonuclear content of 77 per cent. The temperature promptly subsided to normal and remained so. Symptomatic therapy was given, but one month later there had been no particular improvement of the lesions. Starting on May 6, he was given penicillin intramuscularly to a total of 100,000 Oxford units. There was a notable almost immediate response, with complete healing.

He was readmitted on Aug. 24, 1945, with a sore mouth and penile blisters of four or five days' duration. At this time he was only mildly ill, with a temperature of 99.2 F., but there were extensive ulcerations of the buccal mucosa, with some membranous formation, and bullae were present on the penis and one on the skin of the chest. A smear from the mouth showed many fusiform bacilli and a few spirochetes. He was again given penicillin, and by September 6 all lesions had disappeared.

CASE 9.—An 18 year old youth was admitted to the hospital on May 6, 1945, with a history of having had a sore mouth for four days followed by the appearance of red spots and blisters on the chest, arms and penis and subsequently inflamed eyes. He appeared moderately ill and could hardly swallow. His temperature was 99.8 F. There were scattered erythematous lesions, with vesicles and crusting on the skin and penis. Pronounced ulcerations were present on the lips and in the mouth with membranous formation. There was also moderate bilateral conjunctivitis. The

white blood cell count was 10,800, with a polymorphonuclear content of 64 per cent. Culture of material from the throat showed Str. viridans and Staph. aureus, while culture of material from the eyes was sterile. He had had two previous similar episodes, at the ages of 14 and 16 years. He was given penicillin intramuscularly to a total of 460,000 units. His temperature rapidly returned to normal, and by May 23 all lesions had healed. On June 14, while still a patient, he had a recurrence of the lesions, which healed again only to have a fresh crop appear on June 30. On July 5 an ulcer was noted at the anus. When these lesions healed no further recurrences interrupted his convalescence, and he was discharged Aug. 20, 1945.

Fig. 1.—Type of ocular involvement.

Fig. 2.—Balanitis and ulceration.

COMMENT

The accompanying photographs (figs. 1, 2 and 3) illustrate typical lesions of this disease. Figure 1 shows the average type of ocular involvement in the 9 patients who received specific therapy. Note the tenacious membranous exudate in each canthus. Figure 3 *A* shows the bullae on the lips and mucous membrane, which occur early. Figure 3 *B* is of a later stage, when the bullae have ruptured. Figure 2 illustrates penile ulceration and balanitis.

Specifically, the treatment employed consisted in oral use of sulfonamide drugs in 5 patients, in 4 of whom sulfathiazole sesquihydrate drops

or sulfathiazole jelly were employed in the eyes. Three patients were given penicillin intramuscularly, usually with an initial dose of 30,000 Oxford units followed by 20,000 units every three hours to a total of 300,000 units. Penicillin jelly, with 5,000 units to 1 cc. of water-soluble base, was used in the eyes in 1 case. In addition to the use of sulfonamide drugs and penicillin, symptomatic measures were employed, consisting in gentle removal of the membranous conjunctival exudate with boric acid solution at frequent intervals. Hydrogen peroxide was used in a half-strength solution as a mouthwash, and the penile lesions were treated with compresses of sodium bicarbonate.

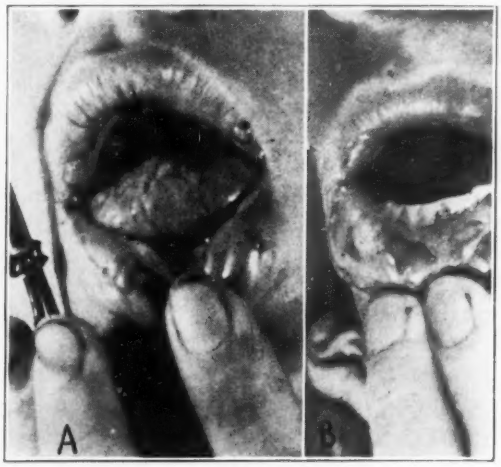

Fig. 3.—*A*, unruptured bullae; *B*, ulcerations from ruptured bullae.

CONCLUSIONS

Nine cases of Stevens-Johnson syndrome have been presented. Five patients were treated with sulfonamide drugs, and 4 patients were treated with penicillin, either systemically or topically or both. Complete recovery without sequelae occurred in all but 1 case. In this case a mild conjunctivitis developed with slight symblepharon but no corneal involvement. Enthusiasm for any type of therapy in this syndrome must be tempered by the fact that the severity of the clinical course varies greatly and that recovery without complications of the eyes is not uncommon. Six of our 9 patients experienced at least one previous attack without permanent ocular damage.

The results of this small series suggest but do not prove that a method of treatment including the use of sulfonamide compounds and/or penicillin might be beneficial in prevention of the tragic complications which so often accompany or follow this disease.

PNEUMONIA IN OLD AGE

Active Immunization Against Pneumonia with Pneumococcus Polysaccharide; Results of a Six Year Study

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EVER since the discovery of the causative agent of pneumonia, its high toll of death has stimulated studies on active immunization against this disease. The experiments, however, when done on human beings were always of short terms. It seemed, therefore, that there was a need for a long term experiment on active immunization against pneumonia. The year by year fluctuations in the incidence and mortality rates might have distorted the results of even the most carefully controlled immunization studies if carried on only for a short period. The perusal of the literature proves that this is exactly what happened; all these experiments, whether done on a large or small scale with vaccines or pneumococcus polysaccharides, were conducted only for one or two years. This is one of the reasons why they contain such contradictory results, contradictory sometimes even within the scope of the same experiment.

Furthermore, it seemed evident from the beginning that if a group was chosen with the highest incidence and mortality rates and with the possibility of continuous observation, hospitalization and reexamination much more conclusive data could be obtained. That was the reason the present study was undertaken in 1937 at the Medical Division of the former Central and Neurological Hospital and the New York City Home and continued at the Goldwater Memorial Hospital, where higher age groups are treated. Within the period of six years it involved about 10,000 persons, immunized and controlled combined, and its purpose, besides immunization of human subjects, was to observe the comparative clinical and pathologic features of pneumonia in the immunized patients

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The pneumococcus polysaccharide used in the latter part of this study was supplied by Dr. Lloyd D. Felton, Medical Director, National Institute of Health, United States Public Health Service, Bethesda, Md.

as compared with those of the disease in the control group, to examine the antigenic effect of the polysaccharides used in this study against experimental pneumococcic infection in mice and to determine the presence of circulating antibodies in those who were immunized.

HISTORY AND LITERATURE OF ACTIVE IMMUNIZATION

Vaccines.—Wright (1913) and others [1] used a nontyped vaccine for immunization against pneumonia in the South African coal mines. The incidence of the disease, as compared with that of the previous year, dropped from 4 to 0.28 per cent and the mortality rate from 0.31 to 0.14 per cent. Maynard [2] (1913) and, later, Lister [3] (1916) used types I, II and III vaccines in the same mines. Both reported a substantial decrease in the incidence and mortality rates. Cecil and his associates [4] (1918, 1920 and 1921) used in three different military camps Whitmore's lipovaccine, an emulsion of types I, II and III pneumococci in oil. The incidence of pneumonia among the inoculated patients was almost one fourth of that among the noninoculated ones.

Further experiments with vaccines on animals have been reported by Barach [5] and Barach and Soroka.[6] Recently, Smillie [7] used types I and II vaccines for the immunization of 590 patients and 40 attendants in an epidemic of pneumonia in the Veterans Administration Hospital at Bedford, Mass. He paid more attention to the epidemiologic and pneumococcus-carrier aspect of the problem. Nevertheless, he felt that the immunization prevented the spread of the epidemic. The vaccine he used was prepared from pneumococci killed by solution of formaldehyde instead of heat, and he used young smooth cultures made with a large amount of inoculum for rapid growth and interrupted before the peak of growth. He gave three injections (0.5, 1.0 and 1.0 cc.) in weekly intervals subcutaneously. No local reaction was noted. Results were encouraging.

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1. Wright, A. E.; Morgan, W. P.; Colebrook, E., and Dodgson, R. W.: Observation on Prophylactic Inoculations Against Pneumococcic Infection, London, 1913; Lancet **1**:87, 1914.

2. Maynard, G. D.: An Enquiry into the Etiology, Manifestations, and Prevention of Pneumonia Amongst Natives on the Rand, Recruited from Tropical Areas, Publication 1, South African Institute for Medical Research, Johannesburg, 1913.

3. Lister, F. S.: Experimental Study of Prophylactic Inoculation Against Pneumococcal Infection in the Rabbit and Man, Publication 8, South African Institute for Medical Research, Johannesburg, 1916.

4. Cecil, R. L., and Austin, J. H.: J. Exper. Med. **28**:19, 1918.

5. Barach, A. L.: J. Exper. Med. **53**:567, 1931; Proc. Soc. Exper. Biol. & Med. **25**:558, 1928.

6. Barach, A. L., and Soroka, M. J.: J. Exper. Med. **48**:83, 1928.

7. Smillie, W. G.: Am. J. Hyg. **24**:532, 1936.

Summarizing the experience of the different authors who used living or killed pneumococci in immunizing human beings and animals, we might say that the results are contradictory. Some authors claimed that the smallest doses usually are sufficient to produce high immunity while high doses stimulate less antibody production, besides causing toxic effects. They reported that in rabbits, after five hours, immune bodies were present in a small degree and that their titer increased after three days, stayed at a peak for one month and was demonstrable for ten months. In mice the immunization succeeded only after large doses had been given subcutaneously or intravenously. In human beings three subcutaneous injections were given in four to eight day intervals, with occasional bad reactions. Most authors noted, besides the specific immunity against types used, protection against other pneumococcic infections. In the experiments on human beings some recorded an apparent decrease in the number of infections of the upper respiratory tract.

Polysaccharides.—Auld [8] and Kraus [9] discovered in the same year (1897), independently, that the germ-free filtrates of certain bacterial cultures contain a substance with antigenic properties—Auld in the cultures of pneumococci and Kraus in cultures of organisms causing typhoid, cholera and bubonic plague. Dochez and Avery [10] (1917) called this substance the "specific soluble substance" and have shown that its presence is due not to bacterial disintegration but to extrusion into the medium of bacterial substances during the life process of the organism. They also demonstrated the presence of this substance in the serum and urine of patients with pneumonia and showed that its presence in abundance indicates a grave prognosis.

Heidelberger and Avery [11] (1923) gave evidence that these nonprotein precipitable substances were polysaccharides and that the combination of the carbon, hydrogen and oxygen to form various percentages of carboxyl, acetyl and other radicals and the combination of these groups with different sugars determine the specificity of the types of pneumococci. They found that the polysaccharide of the type I pneumococci had no antigenic effect, while other authors, with different methods of isolation, demonstrated the antigenic effect of this as well as of the other capsular pneumococcus polysaccharides.[12]

8. Auld, A. G.: Brit. M. J. **1**:775, 1897.

9. Kraus, R.: Wien. klin. Wchnschr. **10**:736, 1897.

10. Dochez, A. R., and Avery, O. T.: J. Exper. Med. **26**:477, 1917.

11. Heidelberger, M., and Avery, O. T.: J. Exper. Med. **38**:73, 1923.

12. Chemically similar substances, i. e., polysaccharides, were isolated by several authors in all sorts of bacteria and found to be serologically active. A partial list follows: Meningococcus; Streptococcus; Gonococcus; Hemophilus influenzae; Pasteurella group; Brucella group; Aerobacter aerogenes; Proteus vulgaris; Bacillus anthracis; spirochetes; Rickettsia, Monilia, Salmonella and Shigella groups; yeasts, and fungi.

Felton in 1932 [13] isolated from pneumococci a water-soluble substance which he found antigenic for mice. He and his collaborators [14] reported later (1938) experiments in immunization on a large number of persons in the Civilian Conservation Camps. The first three experiments were not considered sufficiently controlled to warrant any definite conclusions. In the fourth experiment, inoculations were done on 10,740 men in New England and on 18,494 men in camps on the West Coast. The duration of their observation was short, in some cases 68.3 days and in others 117.4 days.

The incidence rate in the camps on the West Coast was 1.73 in the inoculated persons against 15.96 in the noninoculated group per thousand years of life. The camps in New England showed an incidence of 4.32 per thousand in the inoculated group against 7.28 in the control group. In other words, the incidence in the camps on the West Coast was about nine times higher in the control group than that in the inoculated group, while in the camps in New England it was only about twice as high. According to Felton and his co-workers, "the difference in case ratio between inoculated enrollees in the New England camps and those in the West Coast camps cannot be definitely accounted for." Owing to the circumstances inherent in their experiments, the number of deaths was considered too low to justify any conclusions with regard to the effect of the antigen on the mortality or case fatality rates.

In previous papers,[15] we reported on the results of two years' immunization of 1,750 persons (with 1,870 controls) with types I and II polysaccharides. Among the immunized persons there were 23 patients with pneumonia, making the incidence rate 13.13 per thousand, while among the controls there were 104 patients with pneumonia, with a rate of 55.66 per thousand. The mortality rate in the immunized group was 7.4 per thousand against 35.8 per thousand among the controls.

EXPERIMENTS ON ANIMALS

Methods and Materials.—In the beginning of this study the polysaccharide was prepared by the following method: Broth cultures of type I and type II pneumococci were centrifuged for forty-eight hours. The supernatant fluid was submitted to ultrafiltration. The presence of the soluble specific substance was precipitated by the repeated use of large volumes of alcohol in a reaction which was neutral to slightly acid. The soluble carbohydrates were then tested for their purity and

13. Felton, L. D.: J. Immunol. **23**:405, 1932.

14. Felton, L. D.; Ekwurtzel, G. M.; Simmons, J. S., and Dublin, L. I.: Pub. Health Rep. **53**:1855, 1938.

15. Kaufman, P.; Kaeffely, A.; O'Brien, C.; Burnstein, C.; Kling, S., and Dmitruk, W: Studies on Old Age Pneumonia: Prophylactic Effect of Pneumococcus Polysaccharide Against Pneumonia, Arch. Int. Med. **67**:304 (Feb.) 1941. Kaufman, P.: New York State J. Med. **40**:204, 1940; Bull. New York Acad. Med. **20**:414, 1944.

antigenic properties. The material employed was a combination of types I and II polysaccharides. Chemically, the dextrose and nitrogen content was approximately that of the specific soluble substance of Heidelberger and Avery.

Later a pooled polysaccharide of types I, II and III pneumococci, prepared in the laboratory of the National Institute of Health by Felton, according to his calcium phosphate methods, was used.

To test the antigenic property of this antigen, mice in groups of 20 were given injections of 0.5 cc. of 1:1,000,000 dilution containing 0.0005 mg. of active substance, and eight days later dilution of 1:100; 1:500; 1:1,000; 1:10,000, and 1:100,000 of pneumococcus cultures, representing five million, one million, five hundred thousand, fifty thousand and five thousand lethal doses respectively, were injected intraperitoneally. Protection against type I, type II and type III cultures was tested separately. Results of the titrations can be seen in table 1.

Against type I in dilutions of 1:100 (five million lethal doses) 8 mice out of 20 were protected, while more than 50 per cent of the mice

TABLE 1.—*Antigenic Effect of Types I, II and III Pneumococcus Polysaccharide in Mice*

Titration against 0.5 cc. of dilutions of cultures, specified below, eight days after intraperitoneal injection of 0.5 cc. of 1:1,000,000 dilution of polysaccharide.

Immunized Animals—Rate of Survival Among 20 Inoculated Mice														
Type I Culture Dilutions					Type II Culture Dilutions					Type III Culture Dilutions				
1: 100	1: 500	1: 1,000	1: 10,000	1: 100,000	1: 100	1: 500	1: 1,000	1: 10,000	1: 100,000	1: 100	1: 500	1: 1,000	1: 10,000	1: 100,000
8	**10**	**11**	**13**	**20**	**6**	**8**	**10**	**20**	**20**	**7**	**9**	**11**	**12**	**20**

Control Animals—Hours of Survival Among Controls														
10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}
16	24	22	24	24	18	18	18	20	22	20	24	22	18	20
18	22	24	24	24	20	18	20	22	24	22	24	22	20	22
16	24	24	22	S*	16	18	18	20	S*	22	24	22	18	S*

* S indicates survival of animal.

survived injections of five hundred thousand lethal doses. Protection against cultures of types II and III was somewhat lower, but, generally speaking, protection against all three types was found in 50 per cent of the mice against five hundred thousand lethal doses. The survival time of the nonimmunized animals is given in the lower part of the same table in which the first line represents the culture dilutions (in logarithmic series), the number below them represents the survival time in hours and "survival" indicates survival of the control animals. The figures show that 1 animal survived in the 10^{-9} dilution in all three titrations. The survival time of all other animals varied between sixteen and twenty-two hours.

EXPERIMENTS ON HUMAN BEINGS

Materials.—For human beings the same antigens were used, in the first two years a pooled polysaccharide of types I and II pneumococci and in the following

years a polysaccharide of types I, II and III pneumococci. (For methods of preparation see previous parts of this study and Felton's several publications.[16])

Each year in the pneumonia season a number of persons, selected at random, have been given injections of 0.5 cc. of this substance subcutaneously in the deltoid region. A total of 5,750 were immunized, and 5,153 were kept as controls. The previous history of each person was taken, with special reference to antecedent pneumonia or infection of the upper respiratory tract. On 400 persons taken at random the mouse-protective value of 0.10 cc. of blood serums, withdrawn before and fourteen days after immunization, was tested (for results see following paragraphs). The preliminary work included quantitative and qualitative blood cell counts. We kept records of previous physical examinations, temperature, pulse rate and blood pressure of the immunized persons. Eventual local or general reactions were noted in the protocols, in which the aforementioned data and further information as to the contraction of pneumonia or colds or other diseases were recorded. The records of the controls were handled in the same way. Every person who contracted pneumonia was transferred from the New York City Home

TABLE 2.—*Age Distribution Among the Immunized and Control Group*

Age, Yr.	Immunized Patients (Basis of 5,750), %	Controls (Basis of 5,153), %
Under 40 to 49	1.5	3.9
50 to 59	18.0	19.0
60 to 69	36.5	37.0
70 to 79	30.5	31.6
80 and over	13.5	8.5
Total	100.0	100.0

to Goldwater Memorial Hospital, where it was noted whether he belonged to the immunized or to the control group. Thus the features of the disease and its course, length and outcome in the two groups were observed.

The age distribution in the two groups was about the same, except that there were somewhat more persons in the oldest and somewhat less in the youngest group among the controls. Thirteen per cent were over 80 years, 30 per cent between 70 and 79, 37 per cent between 60 and 69, 18 per cent between 50 and 59 and 2 per cent between 40 and 49 in both groups (table 2). For equalizing purposes, we checked the general mortality rates from all causes except pneumonia in both groups and found that in the immunized group it was 91 and in the control group 89 per thousand.

Results of the Titration of the Blood Serums Before and After Immunizations.—Four hundred persons were selected at random; the only basis of selection was that in age they should be representative of the whole group. About 10 cc. of blood was withdrawn before and fourteen days after immunization and the antibody content tested separately against logarithmic series of dilutions of fresh type I and type II pneumococcus cultures in mice, in the usual manner. As the titrations show in tables 3 and 4, before immunization, protection was

16. Felton, L. D.; Kauffmann, G., and Stahl, H.: J. Bact. **29**:149, 1935. Felton, L. D.; Sutliff, W. D., and Steele, B. F.: J. Infect. Dis. **56**:101, 1935.

afforded against lethal doses with a weighted mean of one hundred and six and after immunization, against one hundred and two thousand, one hundred and seventy lethal doses of type I pneumococci, which means roughly a thousandfold (nine hundred and sixty-four) increase in protection. As regards type II pneumococci, before immunization there

TABLE 3.—*Protective Titer of 0.1 cc. of Human Blood Serums of 400 Persons Before and After Immunization to Type I Pneumococci*

	Before Immunization									
Lethal doses	0	1	10	100	1,000	10,000	100,000	1,000,000		Weighted Mean Lethal Dose,* 106
Persons in each group	265	4	6	5	112	7	1	0	400	Total Positive reactors, 135 (34%) Negative reactors, 265 (66%)
	After Immunization									
Lethal doses	0	1	10	100	1,000	10,000	100,000	1,000,000		Weighted Mean Lethal Dose,* 102,170
Persons in each group	121	0	5	3	18	15	217	21	400	Total Positive reactors, 278 (69%) Negative reactors, 122 (31%)

* Key: Weighted mean lethal dose $= \frac{\Sigma XY}{n}$. Σ indicates the sum total; X, the number of persons in each group; Y, the number of lethal doses, and n, the total number of persons.

was protection against lethal doses with a weighted mean of two hundred and thirty-three; after immunization this showed an increase to seventy-seven thousand, eight hundred and twelve lethal doses (a three hundred and forty-four fold increase).

TABLE 4.—*Protective Titer of 0.1 cc. of Human Blood Serums of 400 Persons Before and After Immunization to Type II Pneumococci*

	Before Immunization									
Lethal doses	0	1	10	100	1,000	10,000	100,000	1,000,000		Weighted Mean Lethal Rose,* 233
Persons in each group	280	3	23	31	60	3	0	0	400	Total Negative reactors, 280 (70%) Positive reactors, 120 (30%)
	After Immunization									
Lethal doses	0	1	10	100	1,000	10,000	100,000	1,000,000		Weighted Mean Lethal Dose,* 77,812
Persons in each group	90	3	0	8	14	21	259	5	400	Total Negative reactors, 90 (23%) Positive reactors, 310 (77%)

* For key, see footnote at bottom of table 3.

Effect of Immunization on the Incidence and Mortality Rates (table 5).—During the period of six years 5,750 persons were immunized and 5,153 observed as controls. There were 99 cases of pneumonia in the first group, meaning an incidence rate of 12.2 per thousand for a six year period. In the control group the number of cases of pneumonia was 227, making an incidence rate of 44 per thousand for a six year period. The mortality rate among the immunized patients was 6.2 per thousand against 19.0 per thousand in the control group, also for a

period of six years. The examination of the figures indicates that there is a great year by year fluctuation in the incidence as well as in the mortality rates of both groups. The significance of this was touched on in the introductory part of this paper and will be elaborated on in the discussion.

TABLE 5.—*Incidence of Pneumonia and Mortality Rates Among Immunized Persons and Controls at Goldwater Memorial Hospital*

	Immunized					Controls				
Year	No. of Immunized Persons	No. of Cases of Pneumonia	Incidence per 1,000	Rates No. of Deaths	Mortality Rates per 1,000	No. of Controls	No. of Cases of Pneumonia	Incidence per 1,000	No. of Deaths	Mortality Rates per 1,000
1st (1937-1938)	1,000	14	14	8	8	1,120	63	56	47	42
2d (1938-1939)	750	9	12	5	6.6	750	41	55	20	26.6
3d (1939-1940)	900	18	20	7	7.7	850	25	29.4	9	10.6
4th (1940-1941)	950	19	20	6	6.3	850	23	27	8	9.4
5th (1941-1942)	1,100	18	16.3	5	4.5	800	38	47.5	8	11.2
6th (1942-1943)	1,050	21	20	9	4.3	783	37	47.2	6	7.6
Totals of 6 yr.	5,750	99	17.2	40	6.2	5,153	227	44	98	19

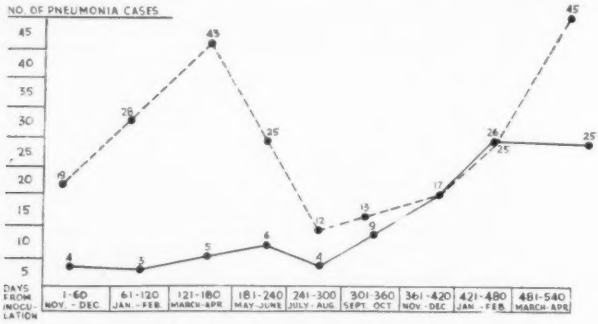
Local and General Reactions.—In 5 per cent of the immunized persons we noted reactions at the site of the injection, evidenced by redness and warmth of the skin. Two in 1,000 (altogether 12) had general reactions in the form of malaise and temperatures between 100 and 101 F. None of these reactions lasted longer than forty-eight hours. Reactions were equal in frequency in the group in which Felton's polysaccharide was injected and in the one in which ours was used.

TABLE 6.—*Length of Protection*

Days from Inoculation to Onset of Pneumonia	Number of Cases	
	Immunized	Controls
November to December..... 1 to 60	4	19
January to February..... 61 to 120	3	28
March to April.....121 to 180	5	43
May to June.....181 to 240	6	25
July to August.....241 to 300	4	12
September to October.....301 to 360	9	13
November to December.....361 to 420	17	17
January to February.....421 to 480	26	25
March to April.....481 to 540	25	45

The Length of Protection.—In table 6 and in the chart the number of days which elapsed between immunization and the onset of pneumonia is plotted against the number of cases of pneumonia in every sixty day period, the basis being the means of six years' figures starting with the months of November to December. Similarly, the mean numbers of cases of pneumonia in the same sixty day periods in the control group are charted. In the immunized group 4 cases of pneumonia occurred

during the first sixty day period and 3 in the next sixty days, and gradually the figures increased in each following period, as can be seen from the almost straight ascending line of the chart. The interrupted line of the chart, representing the control group, shows a different trend, indicating the customary fluctuations in the incidence rate of pneumonia in the different seasons of the year. This confirms the



Interval between immunization and onset of pneumonia. The unbroken line indicates the number of cases of pneumonia as a mean of the six year period in every sixty days after immunization. The broken line indicates the same in the corresponding sixty day periods of the year among the controls.

impression gained from the month by month figures obtained in the first two years of this study, when also comparatively less cases of pneumonia occurred in the first three quarters of the year, after immunizations, than in the later periods.

COMPARISON OF CLINICAL AND PATHOLOGIC FEATURES OF PNEUMONIA IN THE TWO GROUPS

Lobar and Lobular Pneumonias.—There were 27 cases of lobar (8 deaths) and 72 of lobular (23 deaths) pneumonia found in the immunized group. Among the 227 cases of pneumonia among the controls, 67 were cases of lobar pneumonia, with 32 deaths, and 160 were of lobular pneumonia, with 66 deaths.

The Severity of the Disease in the Two Groups.—The following criteria were used to gage the severity of the disease (table 7):

A. Fatality Rates in Cases: The mortality rate in the immunized group was 40 per cent and in the controls 47 per cent, a difference which is statistically without significance.

B. The Extent of the Disease: In the immunized group only one lobe was involved in 23 out of 27 cases of lobar pneumonia (85 per cent) and in 4 cases two or more lobes were consolidated, while among the 67 with lobar pneumonia among the controls in 45 cases (67 per cent) only one lobe and in 22 cases two or more lobes showed roentgenographic signs of consolidation.

C. Bacteremia: Bacteremia was found in 8 cases among the immunized (8 per cent) and in 34 cases among the controls (14.9 per cent; table 9).

D. Duration of the Disease: The average duration of fever in the immunized group was two days in 28 per cent, four days in 32 per cent, eight days in 25 per cent, fourteen days in 10 per cent and more than fourteen days in 5 per cent of the patients who recovered. In the control group the duration of fever was two days in 20 per cent, four days in 27 per cent, eight days in 19 per cent, fourteen days in 23 per cent and more than fourteen days in 16 per cent. The length of time until roentgenologic resolution was completed in the immunized group was one week in 21 per cent, two weeks in 29 per cent, three weeks in 35 per cent, four

TABLE 7.—*Comparative Analysis of Clinical Features in 326 Cases of Pneumonia Among the Immunized Patients and Controls*

	Average Duration of Fever in Patients Who Recovered, Days	Average Time Until Resolution by Roentgen Rays, Wk.	White Blood Cell Count, Average	Average Time for White Blood Cell Count to Come Down Below 8,000, Days	Extent of Process; Lobar or Lobular	Number of Lobes Involved Among Patients with Lobar Pneumonia
Immunized patients (fatality rate 40%)	2 (28%) 4 (32%) 8 (25%) 14 (10%) 14+ (5%)	1 (21%) 2 (29%) 3 (35%) 4 (13%) Unresolved (2%)	15,200	2 (27%) 4 (33%) 8 (21%) 8+ (19%)	27 lobar 72 lobular	1 (23 cases) 1+ (4 cases)
Controls (fatality rate 47%)	2 (20%) 4 (22%) 8 (19%) 14 (23%) 14+ (16%)	1 (15%) 2 (27%) 3 (38%) 4 (15%) Unresolved (5%)	14,800	2 (15%) 4 (29%) 8 (23%) 8+ (33%)	67 lobar 160 lobular	1 (45 cases) 1+ (22 cases)

weeks in 13 per cent; 2 per cent were unresolved. In the control group roentgenologic resolution required one week in 15 per cent, two weeks in 27 per cent, three weeks in 38 per cent and four weeks in 15 per cent; in 5 per cent of the cases the pneumonia was unresolved. In the immunized group the time required for the blood cell count to come down from an average of 15,200 to normal (below 8,000) was two days in 27 per cent, four days in 33 per cent, eight days in 21 per cent and more than eight days in 19 per cent. In the control group it came down from an average of 14,800 to less than 8,000 in two days in 15 per cent, in four days in 29 per cent, in eight days in 23 per cent and in more than eight days in 33 per cent of the cases.

E. Toxemia: Toxemia was found to be strikingly more frequent among the controls than in the immunized group. Abdominal distention was present in 8 per cent of the nonimmunized and in 2 per cent of the immunized group. Circulatory collapse, evidenced by an imperceptible uncountable pulse rate, low blood pressure and clamminess and ashen

color of the skin, was seen in 4 per cent of the controls and in 2 per cent of the immunized group.

COMPARATIVE FREQUENCY OF COMPLICATIONS

No substantial difference was found in the frequency of pleural effusions, empyemas, spontaneous pneumothoraxes and a number of

TABLE 8.—*Comparative Frequency of Complications in Immunized and Control Groups (in Per Cent of Cases of Pneumonia)*

Complications	Immunized Persons, %	Controls, %
Pleural effusions	8	7
Empyema	4	7
Spontaneous pneumothorax	2	3
Atelectasis	3	2
Secondary purulent infection of air passage	5	7
Bronchiectasis	1	1
Unresolved pneumonia	2	5
Formation of pulmonary abscess	1	2
Uremia	3	5
Toxemia	2	6
Relapses	1	4

other complications as listed in table 8. It should be noted, however, that 2 cases of unresolved pneumonia, 2 cases of toxemia and 1 relapse occurred in the immunized group as compared with 5 cases of unresolved pneumonia, 6 cases of toxemia and 4 relapses in the control group.

TABLE 9.—*Distribution of Types Among the Cases of Pneumonia*

Type	99 Immunized		227 Controls	
	Number of Cases	Number of Bacteremias	Number of Cases	Number of Bacteremias
I	1	..	11	4
II	..	..	9	3
III	2	1	13	5
IV	3	1	9	1
V	2	1	7	3
VI	1	..	2	..
VII	2	1	6	2
VIII	3	..	4	2
IX	1	..	2	1
X	..	..	..	..
XI	..	..	..	..
XII	..	..	1	..
XIII	..	..	2	1
XIV	2	1	3	2
XV	..	..	..	..
XVI	1	..	..	..
XVII	..	..	..	..
XVIII	2	..	2	..
XIX	2	1	2	1
All other types	12	2	23	9
Total	34	8	96	34

Types of Pneumococci.—As can be seen from table 9, there were 3 cases of pneumonia caused by types I, II and III pneumococci among the 99 patients with pneumonia in the immunized group, making a rate

of 30.3 per thousand persons. Among the 227 patients with pneumonia in the control group, in 33 cases types I, II and III pneumococci were found, making a rate of 145.3 per thousand persons. Higher types were found in 31 cases in the immunized group (99 cases of pneumonia), making a rate of 313 per thousand persons. In the control group the higher types were found in 63 cases, making a rate of 277 per thousand. In other words, there were considerably more cases of pneumonia caused by types I, II and III pneumococci in the control than in the immunized group, while the percentage of the higher types was somewhat elevated in the immunized as compared with that in the control group.

OBSERVATIONS AT AUTOPSY AMONG THE IMMUNIZED AS COMPARED WITH THE CONTROL GROUP

Twenty-six autopsies were performed on patients who died of pneumonia among the immunized group. The data obtained from 7 of these were published in detail in a preliminary report of this study.[14] From the observations made at these autopsies and at autopsies performed since then, it is evident that there is no appreciable difference between these results and those of 59 autopsies performed among the controls except in two points: in the extent of the process of pneumonia and in the frequency of some of the complications. More than one lobe was involved in 18 per cent of the immunized and in 34 per cent of the control group. Pericarditis was found in 7.2 per cent of the immunized patients and in 16.2 per cent of the controls. No difference was found between the two groups in the percentage of pleural effusions, empyemas, spontaneous pneumothoraxes and atelectasiae. Instances of unresolved pneumonia were found in 2 per cent of the cases in the immunized group at autopsy and in 5 per cent of the cases in the control group.

COMMENTS

This work of six years' immunization against pneumococcic infection submits additional evidence on the antigenic property of the capsular polysaccharide. That property was demonstrated previously by several authors but questioned by others. An effort was made here to eliminate one source of error—the year to year fluctuations of incidence and mortality rates—by continuing the experiments for a longer period. The results seem to corroborate the positive results of previous short term experiments. It is indicated that types I, II and III capsular polysaccharide, used here, gave protection in mice against an average of five hundred thousand lethal doses of homologous cultures, and it lowered the incidence rate of pneumonia in 5,750 immunized persons to 17.2 per thousand as compared with 44 per thousand among approximately the same number of controls. Similarly, it decreased the mortality

rate among the immunized persons to 6.2 per thousand as compared with 19 per thousand among the controls. The incidence of types I, II and III pneumococcic infections was considerably less in the immunized patients than in the control group: 30.3 per thousand against 145.3 per thousand. On the other hand, the percentage of instances of pneumonia caused by pneumococci higher than type III was somewhat elevated in the immunized persons as compared with that in the control group. These data are of significance since the antigen used in this study was in the first two years a type I and II and the following four years a type I, II and III polysaccharide.

In the blood of 400 of the immunized persons an average of a thousandfold increase of the mouse protective titer against type I and a three hundred and forty-four fold increase against type II pneumococci was demonstrated, as compared with the titer before immunization. It should also be noted that a certain percentage of the immunized patients failed to show the presence of antibodies either before or after immunization, an observation first pointed out by Felton, who also indicated that this inability to produce antibodies might have a bearing on the failure of resistance of certain persons to pneumococcic infection.

Attention was focused in this study on the comparative clinical and postmortem features of pneumonia among the immunized patients and the controls.

The question at this phase of the study was this: Did the antigen modify the picture of pneumonia in the group under investigation? The data presented here indicate that in both groups the usual features of pneumonia in old age were found at the bedside as well as on the table at autopsy. There was a difference, however, in certain points; the percentage of bacteremia, toxemia and metastatic invasion of other lobes or organs and the percentage of certain complications were higher among the controls than among the immunized persons. Since the number of cases of pneumonia was not large enough to draw final conclusions, further observations are necessary to answer the aforementioned question.

What is then the practical significance of immunization against pneumonia? Who should be immunized? It is clear that immunization of the general population in the present circumstances would not be practical. There is, however, justification and moreover a necessity for the use of polysaccharides where high incidence rates of pneumonia prevail, as in epidemics, in institutions, especially in homes for the aged, and generally in persons of old age or in those with a tendency to have annually or biannually recurring pneumonia. Even if, as the data presented here indicate, the protection afforded lasts only for ten to twelve months, its application seems to be justified in these cases.

SUMMARY AND CONCLUSIONS

1. The results of immunizations against pneumonia for a period of six years with a polyvalent type I and II and, later, type I, II and III pneumococcus polysaccharide are reported; 5,750 persons were immunized and 5,153 kept as controls.

2. During the total period of observation, the number of cases of pneumonia among the immunized persons was 99, making the incidence rate 17.2 per thousand. Two hundred and twenty-seven cases of pneumonia occurred within the same period in the control group, which equals an incidence rate of 44 per thousand. The number of deaths due to pneumonia in the immunized group was 40, with a mortality rate of 6.2 per thousand as compared with 98 deaths due to pneumonia (making a death rate of 19.0 per thousand) among the controls.

3. The antigenicity of polysaccharides was tested in mice separately against dilutions of types I, II and III pneumococcus cultures. Protection was found against an average of five hundred thousand lethal doses in 50 per cent of the animals.

4. The blood serums of 400 persons of the immunized group showed an average of a thousandfold increase in their protective body titer against type I and a three hundred and forty-four fold increase against type II pneumococcus cultures.

5. The clinical and pathologic picture of pneumonia in the two groups (immunized and controls) was generally the same. There were, however, relatively more bacteremias, toxemias, effusions, empyemas and cases of unresolved and relapsing pneumonia in the controls than in the immunized group. Similarly, there was a difference in the distribution of types in the two groups: more cases of types I, II and III occurred among the controls than among the immunized persons, while the incidence of the higher types was increased in the immunized group as compared with that in the controls.

6. Active immunization in epidemics of pneumonia, in persons in institutions, in elderly persons and in those who have a tendency to recurring pneumonia is suggested.

PRIMARY CARCINOMA OF THE LIVER

A Study of Thirty-One Cases

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PRIMARY carcinoma of the liver is a rare disease. In 1926 Counseller and McIndoe [1] reported 5 instances of this condition in 5,976 necropsies at the Mayo Clinic, and shortly thereafter they reported another.[2] Since that time, 25 additional cases of primary malignant growth of the liver have been discovered at necropsy at the Mayo Clinic. The present study is concerned with these 31 cases.

HISTORIC SURVEY

Rokitansky [3] is credited with being one of the earliest investigators to insist that a primary malignant hepatic neoplasm could occur. In 1876 Kelsh and Kiener [4] reported 2 cases of primary carcinoma of the liver and found only 1 other case in the literature. In 1881 Sabourin [5] added

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Dr. Kernohan is from the Section on Pathologic Anatomy, Mayo Clinic.

An abridgment of this thesis has been submitted by Dr. Hoyne to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of M. S. in Medicine.

We have included only the cases in which the primary carcinomatous growth could be localized definitely within the hepatic substance proper, as arising either from hepatic cells or from the small biliary capillaries. We have excluded any tumors arising from a hepatic duct, either external to the liver, at the porta hepatis or in the short course of this duct within the anatomic confines of the liver itself. We believe that such tumors properly should be classified as "primary carcinomas of the hepatic duct."

1. Counseller, V. S., and McIndoe, A. H.: Primary Carcinoma of the Liver, Arch. Int. Med. **37**:363-387 (March) 1926.

2. McIndoe, A. H., and Counseller, V. S.: Primary Carcinoma of the Liver of Possible Multicentric Origin Occurring in a Case of Portal Cirrhosis, Am. J. Path. **2**:557-567 (Nov.) 1926.

3. Rokitansky, cited by Steiner.[15]

4. Kelsh, A., and Kiener, P. L.: Contribution a l'histoire de l'adénome du foie, Arch. de physiol. norm. et path. **3**:622-656, 1876.

5. Sabourin, C.: Contribution à l'étude des lésions du parenchyme hépatique dans la cirrhose; essai sur l'adénome du foie, Thesis, Paris, no. 39, 1881.

4 more cases. In 1888 Hanot and Gilbert [6] classified the tumors into three macroscopic groups: (1) *cancer nodulaire*, (2) *cancer massif* and (3) *cancer avec cirrhose*. They also suggested the microscopic distinction of *cancer trabéculaire* and *cancer alvéolaire*. In 1901, Eggel,[7] in an extensive and excellent review, collected 162 cases from the literature and added 1 of his own. He disagreed with Hanot and Gilbert's idea of a separate group of *cancer avec cirrhose*, for he noted that cirrhosis also may be found in the nodular and massive forms of carcinoma. Eggel's macroscopic classification still is acceptable: (1) multiple nodular form, (2) solitary massive form and (3) diffuse form. Histologically, Eggel divided the tumors into *carcinoma solidum* and *carcinoma adenomatosum*. In 1911 Goldzieher and von Bókay [8] suggested that the tumors which arise from hepatic cells be called *carcinoma hépatocellulaire* and that those which arise from the epithelium of the smaller bile ducts be known as *carcinoma cholangiocellulaire*. Yamigwa [9] later modified this nomenclature to "hepatoma" and "cholangioma," terms which are generally accepted today.

INCIDENCE

The present group of thirty-one tumors were detected in 16,303 necropsies at the Mayo Clinic, an incidence of 0.19 per cent. Twenty of the lesions were primary carcinomas of hepatic cells, or hepatomas; eleven were primary carcinomas of bile ducts, or cholangiomas.

RACE

We have collected from the literature 339 instances of a primary malignant process of the liver discovered in 159,144 necropsies among American and European peoples. This represents an incidence of 0.227 per cent, or about 1 instance in each 500 necropsies.

There seems to be little doubt that the disease is commoner among the Oriental peoples. A collected series of reports from Asiatic and African institutions revealed that 465 instances of primary carcinoma of the liver had been recorded in 47,292 necropsies. This represents a much higher incidence (0.983 per cent, or nearly 1 instance in each 100 necropsies) than that for European and American peoples.

6. Hanot, V. C., and Gilbert, A.: Études sur les maladies du foie; cancer (épithéliome); sarcome; mélanomes; ystes non parasitaires; angiomes, Paris, Asselin & Houzeau, 1888.

7. Eggel, H.: Ueber das primäre Carcinom der Leber, Beitr. z. path. Anat. u. z. allg. Path. **30**:506-604, 1901.

8. Goldzieher, M., and von Bókay, Z.: Der primäre Leberkrebs, Virchows Arch. f. path. Anat. **203**:75-131, 1911.

9. Yamigwa, K.: Zur Kenntnis des primären parenchymatösen Leberkarzinoms (Hepatoma), Virchows Arch. f. path. Anat. **206**:437-467, 1911.

Among 3,900 specimens obtained in South Africa, Pirie [10] found ninety-one carcinomas of all forms, of which thirty-six were primary carcinomas of the liver. He attributed the high incidence of the disease to the prevalence of schistosomiasis and associated hepatic damage among the natives. The parasite itself was found in 10 of the 36 cases.

Tull [11] has reported from Singapore the largest individual series in the literature—134 cases, of which 126 involved Chinese. The apparent prevalence of these tumors among the Chinese is thought to be due to the high incidence of liver fluke disease (infection with Clonorchis sinensis) in Kwantung, a province of southern China.

Boyce and McFetridge [12] reported that in 18 of their 28 cases the lesion had occurred in American Negroes. However, Lynch [13] observed no such increased incidence among Negroes in his report from Roper Hospital in Charleston, S. C., where the patients are almost exclusively Negroes.

TABLE 1.—*Incidence According to Age in Thirty-One Cases of Primary Carcinoma of the Liver*

Age, Yr.	Lesion	
	Hepatomas	Cholangiomas
1 to 9	1	..
10 to 19	..	..
20 to 29	1	..
30 to 39	..	1
40 to 49	3	3
50 to 59	6	4
60 to 69	7	2
70	2	1
Total	20	11

AGE

Primary carcinoma of the liver is a disease of older age groups; in 60.3 per cent of Eggel's cases the lesion afflicted persons from 41 to 70 years old. In our cases the average age for men was 58.5 years; for women, 48.9 years; for patients who died with hepatomas, 58.7 years, and for those who had cholangiomas, 56.9 years. The incidence according to age in our cases is shown in table 1.

10. Pirie, J. H. H.: Carcinoma of Liver in Natives and Its Frequent Association with Schistosomiasis, M. J. South Africa **17**:87 (Dec.) 1921.

11. Tull, J. C.: Primary Carcinoma of the Liver: A Study of One Hundred and Thirty-Four Cases, J. Path. & Bact. **35**:557-562 (July) 1932.

12. Boyce, F. F., and McFetridge, E. M.: Primary Carcinoma of the Liver: Report of Twenty-Eight Additional Cases, Internat. S. Digest. **18**:67-80 (Aug.) 1934.

13. Lynch, K. M.: Primary Liver Carcinoma: Relation to Yellow Atrophy Cirrhosis, South. M. J. **30**:1043-1049 (Nov.) 1937.

Primary cancer of the liver may occur among children; Noeggerath [14] reported a case in which the lesion was found in a newborn infant. Steiner [15] in 1938 accepted 75 cases from the literature, involving children, as being authentic. Tomlinson and Wolff [16] in 1942 added other reported cases to make a total of 82 authentic cases in which the lesion had afflicted children less than 16 years of age, as described in the literature to that date. In 1 of our cases, primary carcinoma of the hepatic cells attacked a girl 5 years old.

SEX

Primary carcinoma of the liver seems to be predominantly a disease of males. In almost two thirds of Eggel's cases the patients were males, whereas in 23 of our cases (74.2 per cent) the patients were males and only 8 (25.8 per cent) were females.

However, 57.1 per cent of the cancers of the bile ducts in Eggel's series occurred in women. Fried [17] has suggested that this increased tendency toward formation of cholangiomas in women may be caused by the prevalence of infection of the bile ducts followed by inflammatory hyperplasia of the smaller bile ducts. Six of the eleven cholangiomas but only two of the twenty hepatomas in the present series were found in women.

CAUSATION

There seems to be little doubt that chronic irritation of the liver is a prominent causative feature. Twenty-nine of Tull's patients had syphilis, and 6 had malaria. Sanes and MacCallum [18] have reported 2 cases in which cholangioma was associated with hepatolithiasis, cholangitis and cholestasis. Four of our patients drank excessively, 3 had syphilis and 4 were known to have had malaria or typhoid fever. Yamigwa [9] and Ewing [19] suspected that tumors such as those under consideration might arise from embryonic cell rests, but this suspicion never has been confirmed.

14. Noeggerath, E., cited by Steiner.[15]

15. Steiner, M. M.: Primary Carcinoma of the Liver in Childhood: Report of Two Cases with a Critical Review of the Literature, Am. J. Dis. Child. **55**:807-824 (April) 1938.

16. Tomlinson, W. J., and Wolff, E.: Primary Liver-Cell Carcinoma in Infancy: Report of Two Cases, One Showing Calcification, Am. J. Clin. Path. **12**:321-327 (June) 1942.

17. Fried, B. M.: Primary Carcinoma of the Liver, Am. J. M. Sc. **168**:241-267 (Aug.) 1924.

18. Sanes, S., and MacCallum, J. D.: Primary Carcinoma of the Liver: Cholangioma in Hepatolithiasis, Am. J. Path. **18**:675-687 (July) 1942.

19. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 738-753.

PARASITIC INFECTION

Practically all authors from the Orient and Africa stress the causative role of parasitic infection, especially by the liver fluke Clonorchis sinensis and the blood flukes Schistosoma mansoni and Schistosoma japonicum. These parasites are known to damage the liver, and it is believed that this hepatic irritation serves as a precursor for the development of the primary malignant hepatic disease. In a recent publication, however, Hartz [20] wrote that he did not regard schistosomiasis as playing a significant role in the causation of cancer of the hepatic cells in the Chinese.

CIRRHOSIS

A high incidence of cirrhosis accompanying primary carcinoma of the liver has been noted for some time, a coincidence which is unusual when the liver is the seat of metastatic carcinoma. Of 1,989 cases of cirrhosis collected from the literature, Berk and Lieber [21] found 90 (4.5 per cent) in which the condition was associated with primary cancer of the liver.

In the presence of cirrhosis, as in all chronic destructive processes in the liver, there is constant demand for repair. In fact, degeneration, fibrosis, condensation in the bile duct and evidence of regeneration form the cardinal pathologic signs of cirrhosis. Many times this regeneration amounts to an overgrowth, an actual hyperplasia. Eventually, this compensatory hypertrophy may give rise to the formation of multiple hyperplastic nodules, some of which, it is thought, might proceed to become malignant. Of course, what causes one regenerative nodule to remain benign and the other to become malignant is not known. Distinction between the regenerative hyperplasia in certain benign conditions (that is, the "primary toxic necrosis" in case 2 of Wilbur, Wood and Willett [22]) and that which occurs in malignant conditions often is exceedingly difficult. In figure 1 *a* is shown what we consider to be a regenerative hyperplastic nodule of cirrhosis. The decided proliferation, with multinucleated large cells, is apparent and might easily be mistaken for an early primary carcinoma of the hepatic cells.

Because of the extensive vascular growth of the tumor under consideration, pressure atrophy, necrosis and fibrosis adjacent to the tumor often occur. This localized process is unassociated with any diffuse regeneration and must be distinguished from a cirrhotic process.

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20. Hartz, P. H.: Role of Schistosomiasis in the Etiology of Cancer of the Liver in the Chinese, Arch. Path. **39**:1-3 (Jan.) 1945.

21. Berk, J. E., and Lieber, M. M.: Primary Carcinoma of the Liver in Hemochromatosis, Am. J. M. Sc. **202**:708-714 (Nov.) 1941.

22. Wilbur, D. L.; Wood, D. A., and Willett, F. M.: Primary Carcinoma of the Liver, Ann. Int. Med. **20**:453-485 (March) 1944.

In a collected series reported in the literature, in 74.1 per cent of 351 cases hepatoma was associated with cirrhosis, whereas in 131 cases of cholangiomas collected by the same authors only 52.7 per cent of

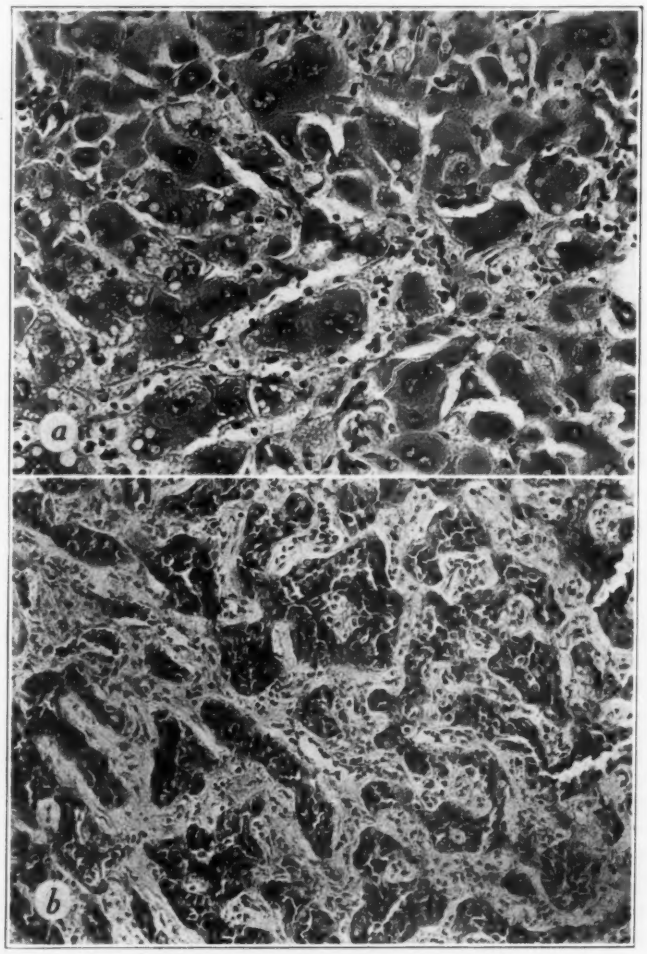

Fig. 1.—(*a*) Histologic section of a nodule from cirrhosis of the liver, showing regenerative hyperplasia and large hepatic cells, many of which are multinucleated. Hematoxylin and eosin. × 200. (*b*) Histologic section of tumorous tissue in case 1, showing the bile duct arrangement of the cells and the abundant connective tissue stroma which are typical of carcinoma of the cells of the bile duct (cholangioma). Hematoxylin and eosin. × 145.

the tumors occurred in association with cirrhosis. In our cases, fifteen of the twenty hepatomas (75 per cent) but only two of the eleven cholangiomas (18.2 per cent) were found in cirrhotic livers.

HEMOCHROMATOSIS

Rowen and Mallory [23] were among the first to suggest that so-called pigmentary cirrhosis might afford an even greater possibility for the development of primary carcinoma than do the other types of cirrhosis.

Sheldon,[24] in his excellent monograph on the subject in 1935, found that in 7.1 per cent of all accepted cases of hemochromatosis in the literature the condition was associated with primary carcinoma of the liver, and he concluded that there is no greater incidence of primary malignant growth of the liver in pigmentary cirrhosis than in nonpigmentary cirrhosis.

Recently, however, Binford, Lawrence and Wollenweber [25] again reviewed the literature and found that twenty-nine primary carcinomas of the liver had occurred in 387 cases of hemochromatosis, an incidence of 7.5 per cent. When Berk and Lieber in 1941 found only ninety primary malignant processes of the liver in 1,989 cases of cirrhosis collected from the literature, they again raised the question of whether hemochromatosis might not be complicated by primary carcinomatous change more frequently than other types of cirrhosis. We shall not attempt to settle the argument. In 1 of our cases, carcinoma of the liver was associated with hemochromatosis.

DIET

Recent experimental work [26] has been done by which it is shown that damage to the liver, cirrhosis and primary cancers can be produced in rats by the feeding of the substance butter yellow, or dimethylaminoazobenzene. Investigators [27] have found that the feeding of rats on diets rich in protein or the amino acids, cystine and choline, together with the vitamin B complex and especially riboflavin, would protect the livers against the formation of tumor. Additional studies are indicated in this regard.

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23. Rowen, H. S., and Mallory, F B.: A Multinucleated Liver Cell Carcinoma, Am. J. Path. **1**:677-680 (Nov.) 1925.

24. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935.

25. Binford, C. H.; Lawrence, R. L., and Wollenweber, H. L.: Hemochromatosis with Primary Carcinoma of the Liver, Arch. Path. **25**:527-533 (April) 1938.

26. Kinosita, R.: Studies on Cancerogenic Chemical Substances, Tr. Soc. path. jap. **27**:665-725, 1937.

27. György, P.; Poling, C. E., and Goldblatt, H.: Necrosis, Cirrhosis and Cancer of Liver in Rats Fed Diet Containing Dimethylaminoazobenzene, Proc. Soc. Exper. Biol. & Med. **47**:41-44 (May) 1941. Miller, J. A.; Miner, D. L.; Rusch, H. P., and Baumann, C. A.: Diet and Hepatic Tumor Formation, Cancer Research **1**:699-708 (Sept.) 1941.

TRAUMA

In a few cases [28] primary carcinoma seems to have been precipitated by an abdominal injury, but development of the malignant lesion may have been purely coincidental.

CLINICAL FEATURES

A review of our own cases and of those in the literature reveals no signs or symptoms pathognomonic to this disease. Ewing has suggested four well defined clinical groups: (1) that in which no symptoms are detected and the patient dies suddenly from hemorrhage or after an illness of a few days, as noted by Karsner [29]; (2) that in which latent carcinoma is found among patients who succumb to cirrhosis or other diseases; (3) that in which the usual history of cirrhosis terminates rapidly with hepatic tumor, jaundice, ascites and cachexia, and (4) that in which the usual history of a malignant tumor, indicating from the first involvement of the liver, develops among previously healthy patients.

The diagnosis is rarely made before the death of the patient. In 1 of our cases the clinical possibility of a primary carcinoma of the liver was entertained. In 8 other cases, the results of biopsy of the liver at the time of surgical exploration were considered to be positive for malignant growth and indicative of primary carcinoma of the liver.

In 27 of our cases (87.1 per cent) and a similarly high percentage of those in the literature, the patients have suffered from weakness and rapid loss of weight. One of our patients, however, had noted a definite gain of weight, which was probably the result of pronounced anasarca throughout the body. Twenty-four of our patients (77.4 per cent) were found to have ascites at necropsy, and in 7 of these patients the ascitic fluid was blood tinged or bloody. The ascites may have resulted from portal obstruction or from metastasis to the peritoneum. Associated edema of the ankles was observed among 23 patients. Twenty-seven of our patients (87.1 per cent) complained of some type of abdominal pain, which varied from minimal distress to severity requiring opiates for relief. Eight of these patients had associated pain in the back, and 6 had pain in the shoulder. Fourteen of our patients (45.2 per cent) had noted nausea and vomiting. Four of these patients had minor bouts of hematemesis, but for none was it a fatal complication. Since a high percentage of the malignant processes in question occur in cirrhotic livers, it might be expected that an occasional patient would die from a ruptured esophageal varix. Only 3 of our patients had specifically complained of diarrhea, and most of them had become increas-

28. Crawford, W. H.: Hypoglycemia with Coma in Case of Primary Carcinoma of the Liver, Am. J. M. Sc. **181**:496-502 (April) 1931.

29. Karsner, H. T.: A Clinicopathological Study of Primary Carcinoma of the Liver, Arch. Int. Med. **8**:238-261 (Aug.) 1911.

ingly constipated. Eighteen of our patients (58.1 per cent) were jaundiced. Jaundice often was mild or moderate, the highest value for serum bilirubin content in our series being 21.7 mg. per hundred cubic centimeters of serum. The van den Bergh reaction frequently is direct, particularly in the higher readings. Tull commented, "It is remarkable that one so often sees a liver actually riddled with new growth, and yet no jaundice." The spleen was palpable in only 6 of our cases (19.4 per cent). Necropsy, however, revealed the spleen to weigh in excess of 300 Gm. in 18 of our 31 cases. That this splenic enlargement is not palpable more frequently may well be due to the commonly associated abdominal distention and ascites. The high incidence of splenomegaly probably is associated with the frequent occurrence of cirrhosis in these cases, but Karsner expressed the opinion that toxemia also may be a factor. Eight patients (25.8 per cent)

TABLE 2.—*Signs and Symptoms in Thirty-One Cases of Primary Carcinoma of the Liver, as Compared with Those in Reports from the Literature*

Sign or Symptom	Percentages According to Series Reported			
	Mayo Clinic	Eggel's [7]	Tull's [11]	Greene *
Weakness	87.1	....	88.8	..
Rapid loss of weight	71	....	....	41
Abdominal distention	87.1	....	....	..
Ascites	77.4	58.5	47	66
Abdominal pain	87.1	....	8.9	29
Nausea and vomiting	45.2	....	2.2	..
Edema of the ankles	74.2	41	84.3	15
Jaundice	58.1	61	34.3	52
Palpable spleen	19.4	32	38.9	34
Dilated superficial abdominal veins	25.8	....	52.2	..
Fever	38.7	14	27.6	..
Palpable abdominal mass	58.1	....	67.9	..

* Greene, J. M.: Internat. Abstr. Surg. **69**: 231, 1939.

had decidedly dilated superficial abdominal veins, a condition which is thought also to be due to the cirrhosis and the attendant portal obstruction. Fever was found in 12 cases (38.7 per cent) and often was a terminal condition. White [30] regarded fever as an exceedingly prominent and suggestive symptom of primary carcinoma of the liver. Wilbur, Wood and Willett, on the other hand, recently reported a case in which hypothermia was consistent and pronounced.

Progressive enlargement of the liver is perhaps the outstanding physical sign. An abdominal mass was palpated in 18 of our 31 cases (58.1 per cent), and in 6 others the liver was enlarged without a definitely palpable tumor. In the other 7 cases the liver was not enlarged, and in 4 of these it was even decreased in size. The largest liver in our series weighed 6,260 Gm. On the basis of the data in table 2 it is apparent that the outstanding signs and symptoms in our cases were

30. White, W. H.: Primary Carcinoma of the Liver, in Allbutt, T. C., and Rolleston, H. D.: A System of Medicine, London, Macmillan & Company, Ltd., 1908, vol. 4, pt. 1, pp. 215-222.

emaciation, abdominal distention with ascites, abdominal pain, edema of the ankles, jaundice and a palpable abdominal tumor.

Nadler and Wolfer [31] were the first to report a case in which spontaneous hypoglycemia had been caused by primary carcinoma of the liver. Crawford [28] and Beers and Morton [32] have since reported similar cases. The pancreas in each case was grossly and microscopically normal. Spontaneous rupture of the liver at the carcinomatous site has been reported as a terminal complication by several authors,[33] but we encountered no such complications.

The laboratory was of little assistance in diagnosis of the condition in these cases. Thirteen patients had varying degrees of anemia, and 7 had leukocytosis ranging in severity up to 26,000 leukocytes per hundred cubic centimeters of blood. Some degree of uremia was present in 11 cases, but this occasionally was only a terminal complication. Tests of hepatic function will indicate hepatic disturbance but not particularly a malignant process. Cunningham [34] has said that elevation of the value for the alkaline phosphatase content of the serum may be especially significant in primary carcinoma of the liver. This test had not been carried out for any of our patients.

Brulé [35] has suggested that fixity of the liver may be an important diagnostic point, and Strong and Pitts [36] expressed the belief that upward movement of the liver, resulting from the fact that the resistance presented by ascites is greater than that of the diaphragm, may be significant. In the present series none of these observations could be made consistently. Mallory's patient (no. 22051)[37] underwent an exploratory operation for suspected mediastinal tumor, which was found to be actually a primary hepatoma pushing the diaphragm high into the

31. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**:700-710 (Nov.) 1929.

32. Beers, D. N., and Morton, J. J.: Primary Carcinoma of the Liver with Hypoglycemia, Am. J. Cancer **24**:51-55 (May) 1935.

33. Mast, W. H., and Streamer, C. W.: Primary Carcinoma of the Liver with Spontaneous Rupture, J. A. M. A. **100**:1684 (May 27) 1933. Schnabel, T. G.: Primary Carcinoma of the Liver with Spontaneous Rupture and Lethal Hemorrhage, Ann. Surg. **101**:613-616 (Jan.) 1935. Jenks, A. L.; Powell, L. D., and Kaump, D. H.: Primary Carcinoma of the Liver with Spontaneous Rupture, J. Iowa M. Soc. **29**:193-197 (May) 1939.

34. Cunningham, R. M.: Primary Carcinoma of the Liver: A Clinical-Pathologic Report of Fourteen Cases at University Hospital from 1927 to 1943, Bull. School Med. Univ. Maryland **28**:61-79 (Oct.) 1943.

35. Brulé, M., cited by Counseller and McIndoe.[1]

36. Strong, G. F., and Pitts, H. H.: Primary Carcinoma of the Liver, Arch. Int. Med. **46**:105-120 (July) 1930; Further Observations on Primary Carcinoma of the Liver in Chinese, Ann. Int. Med. **6**:485-496 (Oct.) 1932.

37. Primary Cancer of Liver, Hepatoma, Cabot Case 22051, New England J. Med. **214**:209-211 (Jan. 30) 1936.

thorax. One of our patients was believed, clinically, to have bronchogenic carcinoma of the lower lobe of the right lung, which was found at necropsy to be extensive pulmonary infarction associated with pulmonary metastasis from a relatively small primary carcinoma of the bile duct.

In summary, we may say that diagnosis of primary carcinoma of the liver in a living person is exceedingly difficult, at best. There are no pathognomonic symptoms, physical signs or decisive observations which can be made in the laboratory or roentgenologically. Biopsy of hepatic tissue offers the best chance for antemortem diagnosis, but many of the patients are in such poor general condition that even this simple procedure is attended with risk.

PATHOLOGIC DATA

Before the diagnosis of primary carcinoma of the liver can be made, it is imperative to search carefully, both grossly and microscopically, for a primary focus. Particular attention in this regard should be paid to the adrenal bodies, kidneys, breasts and gastrointestinal tract. Since the histologic picture of cholangioma resembles so closely that of carcinoma of the extrahepatic bile ducts, the biliary tree and gallbladder must be excluded as a primary focus in all cases.

The proportion of occurrence of primary to secondary carcinoma of the liver has been variously given as 1:64.5 by Hansemann,[38] 1:44 by Counsellor and McIndoe and 1:13.5 by Lisa and Hart.[39] There are no reliable features which will distinguish the two types of carcinoma grossly, although umbilication probably is seen oftener in the metastatic processes than in the primary lesions.

MACROSCOPIC FEATURES

Hanot and Gilbert[6] originally expressed the opinion that it was possible to distinguish clinically between carcinoma of the hepatic cells and carcinoma of the bile duct. Eggel[7] and Karsner[29] did not believe that this was consistently possible. In fact, gross distinction between the two types of carcinoma at necropsy usually is extremely difficult. Ewing has suggested that extensive hemorrhage, necrosis, bulky soft tumorous masses and prominent invasion of the large veins are more likely to occur in the presence of hepatoma but that none of these is pathognomonic.

Eggel described three groupings based on macroscopic appearance, which still may be used: (1) a solitary massive group, in which one

38. Hansemann, D.: Ueber den primären Krebs der Leber, Berl. klin. Wchnschr. **27**:353-356 (April 21) 1890.

39. Lisa, J. R., and Hart, J. F.: Primary Carcinoma of the Liver, New York State J. Med. **38**:1537-1542 (Dec. 15) 1938.

massive nodule may occupy an entire lobe, with numerous smaller tumorous nodules in the adjacent hepatic tissue, (2) a multiple nodular group, in which there are many discrete nodules, varying from a few millimeters to several centimeters, and (3) a diffuse group, in which the entire substance of the liver contains tumorous nodules the size of acini, surrounded by a strong framework of connective tissue. Distinction of the last type from cirrhosis often is possible only with the aid of the microscope.

In 23 per cent of Eggel's cases the lesions were of the massive type, in 64.6 per cent the lesions were multiple nodular and in 12.4 per cent the process was diffuse. In 11 of our cases (35.5 per cent) we found massive tumorous nodules, and in 20 (64.5 per cent) the lesions were classified as "multiple nodular." We had no lesions of the diffuse type, since some degree of nodularity was always apparent.

Ewing and Rolleston and McNee [40] mentioned the frequency with which the primary tumor arises in the right lobe of the liver. In our 11 cases in which massive nodules were present, nine tumors arose in the right lobe, one tumor arose in the left lobe and one arose in the middle of the liver. In the group of multiple nodular lesions, the tumorous masses were present to about equal degree in both lobes.

Ewing has included in his anatomic classification "solitary adenoma or solitary hepatoma." This rare, clinically benign, encapsulated tumor of the liver, which has a varying degree of cellular activity, apparently owes its benignity to its encapsulation. We have no such tumors in this series.

We do not include herein any so-called adenomas of the bile duct, which are small benign malformations of the bile ducts seen not infrequently at necropsy.

Jaffe [41] in 1924 mentioned the fact that 48 cases of primary sarcoma of the liver had been reported previously, in only 29 per cent of which cirrhosis was present. We found no such cases.

The literature contains more reports of hepatomas than reports of cholangiomas, the proportion in our collected series being nearly 3:1 in favor of hepatomas. Wu and Kang [42] suggested that this preponderance of hepatomas may be due to a more active regeneration of hepatic cells than of cells of the bile duct.

Four important features distinguish between hepatoma and cholangioma microscopically (figs. 1 *b*, 2 and 3). These features will be considered next.

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40. Rolleston, H., and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile-Ducts, ed. 3, London, Macmillan & Company, Ltd., 1929, pp. 489-504.

41. Jaffe, R. H.: Sarcoma and Carcinoma of the Liver Following Cirrhosis, Arch. Int. Med. **33**:330-342 (March) 1924.

42. Wu, C. J., and Kang, H. J.: Primary Carcinoma of the Liver, Nat. M. J. China **16**:234-243 (April-June) 1930.

Arrangement of the Cells.—The tumors tend to conform to the structure of the tissue from which they arose. Cancers of the hepatic cells are arranged in cords and may even simulate lobules of hepatic tissue. Rosette-like structures may be seen. Cancers of the bile duct form tubuloalveolar structures (fig 1 *b*) which oftener possess lumens than do tumors of hepatic cells.

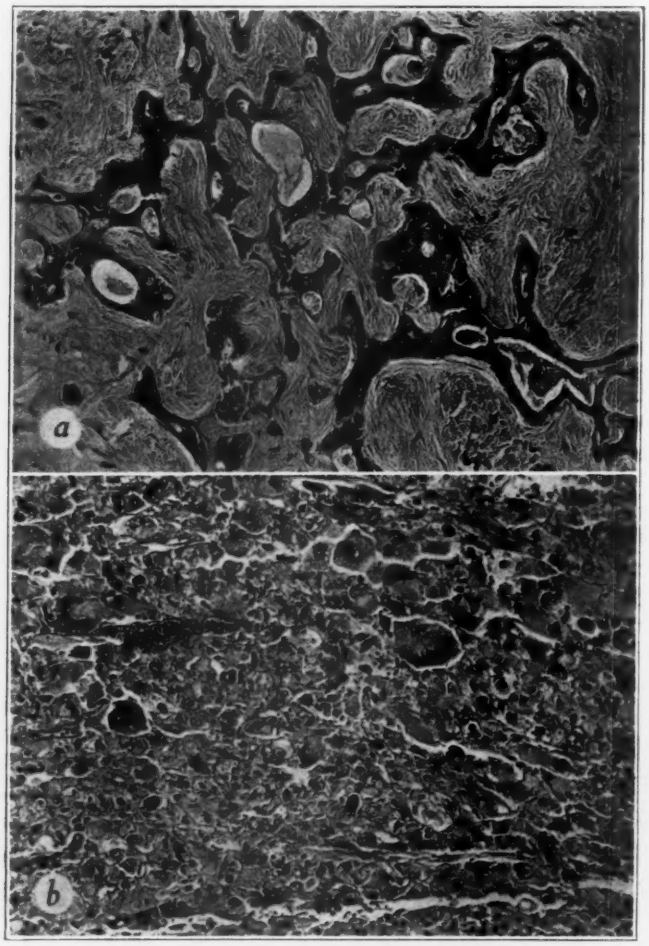

Fig. 2.—(*a*) Histologic section of cholangioma of the liver, showing an increase in fibrous tissue and the arrangement of the tumorous cells simulating bile ducts, with lumens containing hyaline material and cellular debris. Hematoxylin and eosin. × 145. (*b*) Histologic section of the tumorous tissue in case 2, showing the similarity of the tumorous cells to hepatic cells and their arrangement, together with the thin capillary stroma, all of which are the diagnostic criteria of the carcinoma of the hepatic cells (hepatoma). Hematoxylin and eosin. × 145.

Type of the Cells.—The hepatomatous cell is polygonal and polyhedral, with a granular, usually acidophilic cytoplasm which occasionally contains bile. There are large, round, vesicular nuclei which often contain multiple nucleoli. Multinucleated giant cells and atypical bizarre mitosis may be seen (figs. 2*b* and 3*b*), and areas of necrosis occur frequently. The cholangiomatous cell is cuboid or cylindric, with a clear, somewhat basophilic cytoplasm. The nuclei usually are small and hyperchromatic. Giant cells, multiple nucleoli and bizarre types of mitosis infrequently are seen. Most of the tumors in either group would be classified grade 3 or 4 on the basis of Broders' [43] grading, although the hepatomas at first consideration seem to be more active because of the giant cells and bizarre types of mitosis.

Type of Stroma.—The type of stroma is one of the most reliable differential points in cases in which the decision is questionable. The cancer of the hepatic cells has a capillary stroma, whereas the cancer of the bile duct has a connective tissue stroma, with a strong tendency toward cicatricial contraction of the tumorous nodules. This framework of fibrous tissue may be well illustrated by special stains for connective tissue. Either type of lesion may possess a moderate lymphocytic reaction in the stroma, especially if cirrhosis is associated.

Secretion of Bile.—Either type of tumor may be stained deep green by the generalized jaundice and microscopically may exhibit inspissated bile or bile thrombi in the lumens. However, the intracellular existence of bile pigment is considered to be an inherent characteristic of the hepatic cell alone and was thought by Ribbert [44] to be of importance in differential diagnosis. Eggel found intracellular bile pigment in 15 of his 163 cases, and, of these, in 3 there was bile in the metastatic processes. Fox and Bartels,[45] in their study of 80 cases, found bile pigment in fifteen of the primary tumors and in four of the metastatic processes. In our 20 cases of hepatoma, we discovered intracellular bile pigment in 5 cases, in 1 of these the metastatic process, but we did not find it in any of the cases of cholangioma.

Gustafson [46] has reported 2 cases in which neoplastic lesions of both bile duct and parenchymal hepatic cells had occurred, and Pirie found

43. Broders, A. C.: Squamous-Cell Epithelioma of the Lip: A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74**:656-664 (March 6) 1920.

44. Ribbert, H.: Das maligne Adenom der Leber, Deutsche med. Wchnschr. **2**: 1607-1609 (Sept.) 1909.

45. Fox, R. A., and Bartels, G. W.: Primary Carcinoma of the Liver: Report of Three Cases, Arch. Path. **6**:228-239 (Aug.) 1928.

46. Gustafson, E. G.: An Analysis of Sixty-Two Cases of Primary Carcinoma of the Liver Based on 24,400 Necropsies at Bellevue Hospital, Ann. Int. Med. **11**:889-900 (Dec.) 1937.

five such mixed tumors in his 36 cases. Warvi [47] has suggested "cholangiohepatoma" as the best name for this rare condition. It is important that the condensation in the bile duct which accompanies

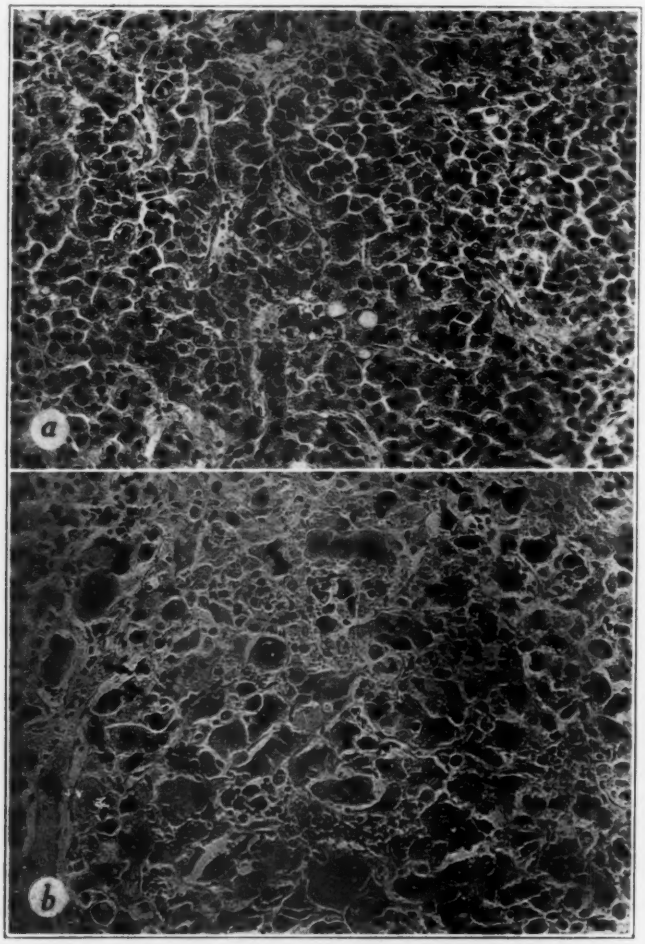

Fig. 3.—(*a*) Histologic section of tissue from a hepatoma; the tumorous cells have a cordlike arrangement, and the capillary stroma is fine. The malignant part of this tumor is much lower than that of the hepatomas seen in figures 2*b* and 3*b;* yet decided destruction of hepatic tissue has occurred. Intracellular bile pigment was seen in parts of this tumor. Hematoxylin and eosin. × 145. (*b*) Histologic section of a hepatoma, showing the resemblance of the tumorous cells to hepatic cells and the fine capillary stroma. Hematoxylin and eosin. × 170.

47. Warvi, W. N.: Primary Neoplasms of the Liver, Arch. Path. **37**:367-382 (June) 1944.

cirrhosis not be considered to be the cholangiomatous portion of this mixed tumor.

MULTICENTRIC VERSUS UNICENTRIC ORIGIN

The question of whether the origin of these tumors is multicentric or unicentric has been argued for years. Goldzieher and von Bókay supported the former view when they could find no direct continuity from one neoplasm to another in careful study of serial sections. Ribbert and, later, Winternitz [48] favored the latter view and stated the belief that the tumor spread intrahepatically from its unicentric origin by way of its early invasion of the portal system. A majority of authors now seem to believe, with Loesch,[49] that most of these tumors arise unicentrically, although multicentric origin may occur rarely in some cirrhotic livers. One of our cases was previously reported by McIndoe and Counseller [2] as an example of possible multicentric origin of the tumors.

EXTENSION

The secondary spread of primary carcinoma of the liver takes place by direct extension and by metastasis through the blood and lymph channels. The hepatomatous cells early invade the smaller radicles of the portal vein, thus causing rapid dissemination of the malignant nodules throughout the liver. The hepatomatous cells may grossly invade the efferent veins from the liver as well (fig. 4). Eggel found tumorous thrombosis in the large veins in 35 of his 163 cases. Simpson [50] in 1924 studied 78 cases of tumorous thrombosis of the inferior vena cava and found that in 7 (10 per cent) cases the condition had been caused by primary carcinoma of the liver.

Gregory [51] in 1939 studied 12 cases of primary carcinoma of the liver with tumorous thrombosis of the inferior vena cava. The two outstanding physical manifestations, he noted, were swelling of the patients' lower extremities and ascites. The tumorous thrombosis may extend into the right auricle and thereby cause symptoms of cardiac failure. Small pulmonary emboli from these thrombotic processes may be observed microscopically.

In no cases of cholangioma was there invasion of blood vessels. In 8 of the 20 cases of hepatoma, the tumor had invaded only the smaller branches of the portal and hepatic veins, but in 2 of these tumorous

48. Winternitz, M. C.: Primary Carcinoma of the Liver, Johns Hopkins Hosp. Rep. **17**:143-184, 1916.

49. Loesch, J.: Primary Carcinoma of the Liver, Arch. Path. **28**:223-235 (Aug.) 1939.

50. Simpson, W. M.: Tumor-Thrombosis of Inferior Vena Cava, with Four Additional Cases of Neoplastic Invasion, Ann. Clin. Med. **3**:29-68 (July) 1924.

51. Gregory, R.: Primary Carcinoma of the Liver: Tumor Thrombosis of the Inferior Vena Cava and Right Auricle, Arch. Int. Med. **64**:566-578 (Sept.) 1939.

emboli were found microscopically in the lungs. In 2 other cases tumorous thrombosis of the portal and hepatic veins had extended into the inferior vena cava and right auricle. In another case (case 2) tumorous thrombosis of the hepatic vein and inferior vena cava was complicated by retrograde thrombosis of the left renal vein and by uremia.

Ewing mentioned the fact that extrahepatic metastasis is seen earlier and more frequently in cancers arising from the small bile ducts than

Fig. 4.—Large tumorous thrombosis of the hepatic vein and inferior vena cava in case 2.

in those arising from the hepatic cells. This discrepancy is hard to explain when the much more prominent invasion of blood vessels by hepatomas is considered. We found extrahepatic metastasis to be present in 21 of our 31 cases (67.7 per cent). However, in only 11 of our 20 cases of hepatoma (55 per cent) was there distal metastasis, whereas in 10 of our 11 cases of cholangioma (91 per cent) there was distal metastasis, facts which tend to support Ewing's impression. It is apparent, on the basis of table 3, that distal metastasis in our cases occurred most frequently in the regional lymph nodes and the lungs.

Charache,[52] in his review of the literature in 1939, found 18 cases in which skeletal metastasis had occurred, an incidence of 1.6 per cent of all cases of primary carcinoma of the liver. In 3 of our cases bony metastasis had occurred, and in each case the metastatic process was situated in the spinal column.

PROGNOSIS AND TREATMENT

The tumors under consideration grow exceedingly rapidly. Most of the patients die within a few months after the onset of the symptoms. The only possible treatment is surgical resection of the liver, which is performed with great risk and oftenest unsuccessfully. Keen [53] in 1899

TABLE 3.—*Sites of Sixty-One Extrahepatic Metastatic Processes in Thirty-One Cases of Primary Carcinoma of the Liver*

Metastatic Process, Site	Type of Tumor		
	Hepatic Cell (30 Cases)	Bile Duct Cell (11 Cases)	Total
Periportal lymph nodes	6	8	14
Lung	9	4	13
Mediastinal lymph nodes	3	3	6
Peritoneum	1	2	3
Diaphragm	2	2	4
Omentum	2	1	3
Stomach (by direct extension)	0	1	1
Duodenum (by direct extension)	1	0	1
Gallbladder (by direct extension)	0	2	2
Pancreas	1	2	3
Spleen	0	2	2
Adrenal glands	2	3	5
Ureter	0	1	1
Vertebra	1	2	3
Sites, total	28	33	61

collected 76 cases in which the liver had been resected for a neoplastic condition, with an immediate fatality rate of 14.9 per cent. Yeomans [54] in 1915 reported a second unsuccessful operation for recurrent primary carcinoma of the liver, the original tumor of which had been successfully removed, first, seven years before. Wallace [55] in 1941 collected 29 cases of "removable hepatoma" from the literature and added a case

52. Charache, H.: Primary Carcinoma of the Liver: Report of a Case and Review of the Literature, Am. J. Surg. **43**:96-105 (Jan.) 1939.

53. Keen, W. W.: Report of a Case of Resection of the Liver for the Removal of a Neoplasm, with a Table of Seventy-Six Cases of Resection of the Liver for Hepatic Tumors, Ann. Surg. **30**:267-283 (Sept.) 1899.

54. Yeomans, F. C.: Primary Carcinoma of the Liver, with Report of a Patient Who Remained Well Over Two Years After Operation, J. A. M. A. **52**:1741-1743 (May 29) 1909; Primary Carcinoma of the Liver: Operation for Recurrence Over Seven Years After Primary Operation, ibid. **64**:1301-1303 (April 17) 1915.

55. Wallace, R. H.: Resection of Liver for Hepatoma, Arch. Surg. **43**:14-20 (July) 1941.

of his own. Most authors agree with Yeomans that "the only hope for improvement in results lies in the direction of earlier operative exploration in patients with tumors in the right upper quadrant in whom no primary growth can be found elsewhere in the abdomen."

REPORT OF CASES

CASE 1.—A man 59 years old was admitted to the clinic on Dec. 26, 1931 because of sharp pain in the lower part of the thorax on the right side. This pain was aggravated by breathing. It had been present for three weeks. The patient had used alcohol excessively until three years before the time of his registration. Results of a general physical examination at this time were essentially normal. Results of urinalysis and blood cell counts were normal. Roentgenograms of the thorax and roentgenoscopic examination of the stomach disclosed nothing significant. A cholecystogram revealed a "poorly functioning gallbladder." The patient's pain increased in severity, and he lost 20 pounds (9 Kg.) in the next three weeks. A sulfobromophthalein excretion test of hepatic function revealed retention of dye, grade 4. The serum bilirubin content measured 1.2 mg. per hundred cubic centimeters of serum and gave the indirect van den Bergh reaction. The liver rapidly increased in size and felt nodular and extremely hard. Ascites became increasingly evident. A second roentgenogram of the thorax was reported as showing "infiltration of the right base and a small amount of fluid in the right base." Another leukocyte count amounted to 17,400 per cubic millimeter of blood. The value for blood urea was 32 mg. per hundred cubic centimeters of blood. The patient failed rapidly, and he died three months after registration. The clinical diagnosis was cirrhosis, metastatic malignant growth of the liver or possible primary cancer of the liver after long-standing cirrhosis.

Necropsy was performed two hours after death of this patient. The report was primary carcinoma of the liver with metastasis to the spleen and the lymph nodes; edema of the lungs with bronchopneumonia; ascites and bilateral hydrothorax; hemorrhage occurring into the wall of the stomach; cholelithiasis (eleven stones); hypertrophy of the prostate gland, grade 2; two diverticula of the urinary bladder; healed tuberculosis of the hilar lymph nodes, and arteriosclerosis of grade 2.

The skin was jaundiced to grade 1, and edema of the legs, grade 1, was noticed. The peritoneal cavity contained 2,500 cc. of turbid brownish fluid, but there were no signs of peritonitis. There was about 100 cc. of straw-colored fluid in each pleural cavity. The spleen weighed 298 Gm.; on the cut surface were seen many firm white-yellow nodules up to 0.3 cm. in diameter. The gallbladder contained 50 cc. of thick tarry bile and eleven small mulberry stones. The mucosa exhibited cholesterosis of grade 1. The extrahepatic bile ducts, pancreas and duodenum appeared to be normal. The lesser curvature of the stomach was firmly attached to the liver. The stomach contained 150 cc. of reddish brown fluid, and the mucous membrane was diffusely congested. Along the lesser curvature of the stomach were several enlarged firm lymph nodes which appeared to contain metastatic carcinoma. The liver weighed 3,782 Gm. and was covered with rough whitish nodules up to 5 cm. in diameter (fig. 5). Several of these nodules were umbilicated. The consistency of the liver was increased to grade 3. The cut surface of the liver was studded with malignant whitish yellow nodules, which had destroyed about two thirds of the hepatic parenchymatous tissue. The left lobe of the liver was decreased in size. There was no gross invasion of the larger portal or hepatic veins.

Microscopic sections (fig. 1*b*) showed extensive invasion of the hepatic parenchyma by the malignant process. The cuboid to cylindric cells, with dark pyknotic nuclei and clear cytoplasm, were arranged in tubular form. In some areas the growth was less differentiated and more anaplastic; in these areas more mitotic figures were seen. The lumens of the alveoli were relatively small. They contained amorphous material and cellular debris. An abundant connective tissue stroma, containing relatively few lymphocytes, separated the alveolar elements. Many small blood vessels filled with blood were seen. The neoplasm appeared to be rather vascular and certainly of a high grade of malignancy. The hepatic parenchyma itself appeared to be normal, save for some amount of inspissated bile in the small biliary canaliculi. There was no evidence of cirrhosis. Histologically, this tumor was a cholangioma.

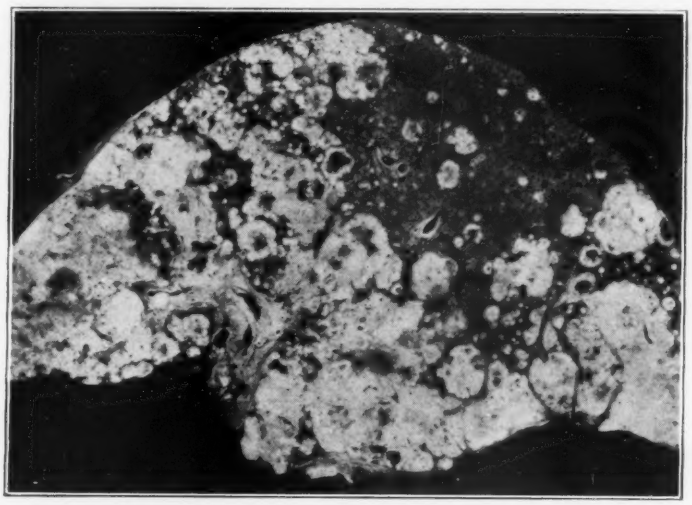

Fig. 5.—The liver in case 1. Note the multiple tumorous nodules throughout both lobes of the liver. Cirrhosis is not present.

Case 2.—A man 57 years old was admitted to the clinic on May 25, 1933, complaining of a progressively growing ulcer on the lower lip. Results of physical examination otherwise were essentially normal. Blood cell counts were within normal limits, but urinalysis disclosed glycosuria. The value for fasting blood sugar content was 94 mg. per hundred cubic centimeters of blood, but the glucose tolerance curve was indicative of mild diabetes mellitus. The ulcerated labial lesion was excised; the pathologic report was "squamous cell epithelioma, grade 3." Later, dissection of the submental, submaxillary and upper jugular lymph nodes was performed; pathologic examination of these nodes did not show metastatic carcinoma. Convalescence of the patient was uneventful.

This patient returned on March 15, 1943. He was admitted directly to the hospital in a critical condition. For three months he had noted weakness, loss of weight and anorexia. His local physician had suspected gastric ulcer, but treatment with diet and alkaline powders had failed to help. He had become semistuporous and edematous within the preceding forty-eight hours.

Physical examination showed a dehydrated semistuporous man, whose breath had the odor characteristic of uremia. The systolic blood pressure measured 140 and the diastolic 70 mm. of mercury. The heart and lungs were normal. No abdominal masses were palpable. The prostate gland was slightly enlarged. Noticeable pitting edema of both lower extremities and abdomen was observed.

Urinalysis disclosed albuminuria of grade 2, no glycosuria and hyaline casts, grade 3. The hemoglobin content measured 11.2 Gm. per hundred cubic centimeters of blood, and the erythrocytes numbered 3,120,000 per cubic millimeter of blood. The leukocyte count was 15,300 per cubic millimeter of blood, and the differential blood count was as follows: segmented neutrophils 45, "band forms" 41, lymphocytes 9 and monocytes 5. Results of the flocculation test for syphilis were negative. A roentgenogram of the thorax demonstrated no abnormality. Data concerning

Fig. 6.—The liver in case 2. Note the large tumorous mass in the right lobe of the liver, with smaller satellite nodules around the periphery. Cirrhosis is distinct.

blood chemistry were as follows: urea content 266, creatinine content 2.6 and sugar content 147 mg. per hundred cubic centimeters of blood; chloride content 518, cholesterol level 66 mg., per hundred cubic centimeters of plasma, and calcium content 8.4 mg. per hundred cubic centimeters of serum. The carbon dioxide–combining power was 43.8 volumes per cent. The serum protein content measured 5.56 Gm. per hundred cubic centimeters of serum, and the albumin-globulin ratio was 1.18: 1.

The course of this patient was rapidly downhill. He lapsed into a profound coma, had a terminal bout of hematemesis and died four days after his arrival at the hospital. The prevailing clinical diagnosis was uremia, possibly on the basis of chronic nephritis.

Necropsy was performed twelve hours after the death of the patient. The report was cirrhosis of the liver, with malignant hepatoma invading the hepatic

vein and inferior vena cava; tumorous thrombosis of the lower vena cava and left renal vein; ascites; ruptured esophageal varices, with residual hemorrhage in the stomach; healing duodenal ulcer, with partial pyloric obstruction; edema and emphysema of the left lung, with beginning pneumonia; grade 2 hypertrophy of the prostate gland; small calculus in the urinary bladder, with cystitis cystica of grade 2; two polyps and two lipomas of the cecum, and arteriosclerosis of grade 2.

There was edema of grade 3 of both lower extremities and of the entire back. The peritoneal cavity contained 2,000 cc. of cloudy amber fluid, but there were no signs of peritonitis. The spleen weighed 144 Gm. It appeared to be normal. The gallbladder contained 40 cc. of bile, and the mucosa appeared normal. The extrahepatic bile ducts and pancreas seemed to be normal. The esophagus contained several dilated and ruptured varices and a few superficial longitudinal ulcers. The stomach contained 350 cc. of clotted blood and mucus. The duodenum was somewhat narrowed by a healing ulcer situated 1.5 cm. below the pylorus. The liver weighed 2,008 Gm. The surface was irregularly nodular and granular. The consistency was increased to grade 2. The cut surface was gray-yellow, and the markings were indistinct. Within the substance of the right lobe there was a soft yellowish pink mass measuring 5 by 7 cm. and surrounded by several smaller similar masses up to 1.5 cm. in diameter (fig. 6). The hepatic vein and the inferior vena cava were completely filled with an adherent thrombus which extended 1 cm. into the left renal vein and narrowed it about 50 per cent. No thrombus was found in the right auricle.

Histologic sections (fig. 2 *b*) showed an extensive amount of tumorous tissue, which was necrotic and hemorrhagic in some areas. The large polyhedral polygonal cells with vacuolated acidophilic cytoplasm and large, vesicular, frequently multiple nuclei and nucleoli were arranged in trabecular fashion and in cords. There were numerous multinucleated tumorous giant cells and many typical and bizarre mitotic figures. No evidence of intracellular bile pigment was discovered. Blood vessels were prominent, and the tumor appeared to be exceedingly vascular. The stroma was of the capillary type and contained numerous lymphocytes, especially near the hepatic parenchyma. Certain sections showed prominent invasion of the larger blood vessels by the tumorous cells. The hepatic parenchymatous tissue had been replaced by considerable dense fibrous tissue containing many bile ducts and lymphocytes. Numerous large and small regenerative nodules were seen to possess no biliary canaliculi or central veins. Histologically, this tumor was a highly malignant hepatoma, occurring in a decidedly cirrhotic liver.

SUMMARY AND CONCLUSIONS

Primary carcinoma of the liver is a rare disease. Thirty-one instances have been found in 16,303 necropsies at the Mayo Clinic, an incidence of 0.19 per cent. Six of the cases had been previously reported in the literature. The disease occurs most commonly in the Orient and South Africa. A series of reports collected from the literature reveals an incidence of 0.227 per cent among the white-skinned races of Europe and America and an incidence of 0.983 per cent among the Asiatic and African races. This increased tendency of the disease to afflict the latter peoples is believed to be due to the high geographic incidence of schistosomiasis and clonorchiasis among them and to the chronic irritation of the liver caused by these parasitic infections. Primary

carcinoma of the liver is a disease of older persons. In most of our cases the lesion occurred in the fifth, sixth and seventh decades of life. In 23 of our 31 cases the disease occurred in males, the sex which usually is more frequently afflicted. The primary carcinomas of the liver arising from hepatic cells are called "hepatomas," and those arising from bile ductules are called "cholangiomas." Reports of hepatomas in the literature far exceed those of cholangiomas. In 20 of our 31 cases the tumors were hepatomas, and in 11 they were cholangiomas. Cirrhosis frequently is associated with primary carcinoma of the liver and undoubtedly is an important causative factor. In 16 of our 20 cases of hepatomas (75 per cent) cirrhosis was associated, but it was present in only 2 of our 11 cases of cholangiomas (18.2 per cent). It is still debatable whether the incidence of primary carcinoma of the liver is any greater in the presence of hemochromatosis than it is when nonpigmentary cirrhosis alone is present. There are no pathognomonic clinical or laboratory signs or symptoms in these cases, and the diagnosis is rarely made before the death of the patient. The most significant symptoms and signs in our cases were emaciation, abdominal distention with ascites, abdominal pain, edema of the ankles, jaundice and a palpable abdominal tumor.

Gross distinction between hepatoma and cholangioma usually is difficult, and the final diagnosis must be made histologically. The question of multicentric or unicentric origin of these tumors is still debatable; most authors favor the latter view. Eleven of our 20 cases of hepatomas were characterized by obvious invasion of blood vessels. The early vascular involvement is thought to cause the intrahepatic metastasis so often seen in the presence of hepatoma. Tumorous thrombosis of the inferior vena cava and right auricle may accompany these tumors. In 21 of our 31 cases (67.7 per cent) extrahepatic metastasis was present. Cholangioma as a rule metastasizes earlier and more frequently than does hepatoma. The tumors under consideration grow exceedingly rapidly, and the prognosis usually is hopeless. Early surgical resection of the liver offers the only chance for cure.

HOMOLOGOUS SERUM HEPATITIS FOLLOWING TRANSFUSION

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JAUNDICE was an important medical problem in the European Theater of Operations after the American troops arrived in Northern Ireland and England in the early months of 1942. Until the late summer and fall of 1944 this jaundice was considered to be for the most part due to either infectious hepatitis or homologous serum hepatitis following the injection of yellow fever vaccine. In contrast, in many cases the jaundice seen following the invasion of Normandy, though belonging to the homologous serum group, differed in that the disease was transmitted by plasma, serum or whole blood instead of vaccine containing a human serum component.

With the ever increasing use of transfusions of blood and plasma, it seems pertinent to emphasize the occurrence and importance of homologous serum hepatitis following this therapeutic procedure. It is the purpose of this paper to review briefly some of the literature and to report a series of 14 cases of homologous serum hepatitis, with a detailed description of the 2 fatal ones and the important findings at autopsy.

The entity of homologus serum jaundice was first described by Lürman in 1885, in reporting the outbreak of jaundice among workers in a Bremen shipyard who had been vaccinated with a vaccine containing human lymph. From one to seven months after vaccination 191 out of 1,289 persons became jaundiced, while 500 other workers in the same shipyard, vaccinated with a different lot of lymph, remained free of the disease. No further report of jaundice following the use of human serum products appeared until 1937, when the phenomenon was reported by Findlay and MacCallum [1] as occurring in a number of persons several months after they had been inoculated with a yellow fever vaccine containing human serum. This was followed in 1938 by MacNalty's [2] report, in which he described similar cases in groups

When this paper was written Dr. Ginsberg held the rank of Major in the Medical Corps of the Army of the United States.

1. Findlay, G. M., and McCallum, F. O.: Note on Acute Hepatitis and Yellow Fever Immunization, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:297, 1937.

2. MacNalty, A. S.: Report of the Chief Medical Officer, Ministry of Health, London, His Majesty's Stationery Office, 1938.

of children given injections of pooled measles convalescent serum. In recent years there have been numerous articles recording cases of jaundice following injection of yellow fever vaccine in England,[3] the United States,[4] Brazil [5] and the Virgin Islands [6]; mumps and measles convalescent plasma and serum in England,[7] and pappataci fever vaccine in Russia.[8] The period of incubation in these cases ranged between thirty-five and one hundred and forty days, in the great majority being sixty to ninety days.

Morgan and Williamson [8] subsequently reported 9 cases of jaundice occurring seven to sixteen weeks after transfusions of plasma or serum, and Beeson [8a] has recorded the occurrence in 7 patients one to four months following transfusions of blood or plasma.[9] Bradley and

3. (*a*) Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization, Lancet **1**:678, 1943. (*b*) Homologous Serum Jaundice, Memorandum Prepared by Medical Officers of Ministry of Health, ibid. **1**:83, 1943. (*c*) Findlay and MacCallum.[1]

4. (*a*) Outbreak of Jaundice in Army, Circular Letter No. 95, Office of the Surgeon General, J. A. M. A. **120**:51 (Sept. 5) 1942. (*b*) Jaundice Following Yellow Fever Vaccination, editorial, ibid. **119**:1110 (Aug. 1) 1942. (*c*) Turner, R. H.; Snavely, J. R.; Grossman, E. B.; Buchanan, R. N., and Foster, S. O.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine: Especial Consideration of Severe Attacks, Ann. Int. Med. **20**:193, 1944.

5. Fox, J. P.; Manso, C.; Penna, H. A., and Para, M.: Observations on Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68, 1942.

6. Findlay and Martin.[3a] Fox and others.[5]

7. (*a*) Beeson, P. B.; Chesney, G., and McFarlan, A. M.: Hepatitis Following Injections of Mumps Convalescent Serum: I. Use of Plasma in the Mumps Epidemic, Lancet **1**:814, 1944. (*b*) Hawley, W. L., and others: Hepatitis Following Injection of Mumps Convalescent Plasma: III. Clinical and Laboratory Study, ibid. **1**:818, 1944. (*c*) McFarlan, A. M., and Chesney, G.: Hepatitis Following Injection of Mumps Convalescent Plasma: II. Epidemiology of the Hepatitis, ibid. **1**:816, 1944. (*d*) MacNalty.[2] (*e*) Footnote 3 *b*.

8. Morgan, N. V., and Williamson, D. A. J.: Jaundice Following the Administration of Human Blood Products, Brit. M. J. **1**:750, 1943.

8a. Beeson, P. B.: Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma, J. A. M. A. **121**:1332 (April 24) 1943.

9. Since this paper was prepared and submitted to the Surgeon General's Office for approval for publication there have appeared two articles of a similar nature to this paper. E. M. Rappaport (Hepatitis Following Blood or Plasma Transfusions: Observations in Thirty-Three Cases, J. A. M. A. **128**:932 [July 28] 1945) reported 32 patients evacuated from theaters of combat in whom hepatitis developed nine to eighteen weeks following transfusions of blood or plasma. There were no fatalities. A. M. Snell, D. A. Wood and L. J. Meienberg (Infectious Hepatitis with Especial Reference to Its Occurrence in Wounded Men, Gastroenterology **5**:241, 1945) presented the findings of 32 patients in whom hepatitis developed in twenty-one to one hundred and forty days, with an average

others [10] have recently demonstrated, by the use of reconstituted human serum containing an icterogenic agent, that the length of the period of incubation and the severity of the disease are not appreciably influenced by the amount of serum administered or the parenteral route used. They gave injections in one group of patients using 0.1 cc. of serum intradermally, in a second using 400 cc. intravenously and in a third using both. In 57 per cent of the persons to whom injections were given hepatitis developed, and there were no significant variations in the severity of the disease or the length of the period of incubation.

The aforementioned clinical reports have been paralleled by experimental transmission of the disease to human volunteers, known icterogenic lots of vaccine having been employed and serum, blood or plasma from patients in the early stages of this disease.[11] Findlay and Martin [3a] claimed transmission of the disease by the use of nasal washings obtained from 3 patients in the preicteric stage of jaundice caused by post-yellow-fever vaccine. In their studies, the instillation of the filtered washings into the noses of 4 volunteers resulted in 3 cases of hepatitis.

MATERIAL

From Sept. 18, 1944 to Nov. 14, 1944 there were observed at the Seventh General Hospital 14 cases of hepatitis believed to be the result of transfusions of plasma administered forty-five to eighty-eight days before the onset of symptoms. Twelve of the patients were studied throughout the course; 1 arrived from a nearby station hospital three days after the onset of his jaundice and while still having acute symptoms, and 1 arrived from a general hospital in France three weeks after the onset of his jaundice and during his convalescent stage.

Twelve of these patients were battle casualties from France being treated for or convalescing from wounds received in combat. The remaining 2 received injuries in England, 1 a ruptured liver and the other a perforated hollow abdominal viscus. All had been continuously hospitalized since their injuries.

SUMMARY OF SERIES

Period of Incubation.—The period of incubation of the disease in this series, as determined from the date on which plasma or blood was first administered to the onset of symptoms, ranged from forty-three to eighty-eight days, with an average of sixty-three days (table 1). All

of eighty-four days, following transfusions of blood and plasma. In 8 patients in this series there developed symptoms and signs of severe disease of the liver and involvement of the central nervous system, 6 of whom died. The mortality rate of 19 per cent is comparable to that of 15 per cent in our smaller series.

10. Bradley, W. H.; Loutit, J. F., and Maunsell, K.: An Episode of Homologous Serum Jaundice, Brit. M. J. **2:** 268, 1944.

11. (*a*) MacCallum, F. O., and Bauer, J. J.: Homologous Serum Jaundice: Transmission Experiments with Human Volunteers, Lancet **1:**622, 1944. (*b*) Oliphant, J. W.; Gilliam, A. G., and Larson, C. L.: Jaundice Following Administration of Human Serum, Pub. Health Rep. **58:**1233, 1943. (*c*) Oliphant, J. R.: Jaundice Following Administration of Human Serum, Bull. New York Acad. Med. **20:**429, 1944.

patients had received plasma or serum, and in addition 9 had had blood transfusions.

Clinical Picture.—The initial symptoms were usually malaise, lassitude, ease of fatigue, anorexia, low grade fever (only 4 patients having a temperature of 100 F. [orally] or over), chilliness, headache and generalized aches and pains in the joints. These symptoms were soon followed by nausea, often accompanied with vomiting, abdominal discomfort or pain, which was frequently localized by the patient in the epigastrium or periumbilical region, and change of bowel habits, constipation being more frequent than diarrhea. The patient usually noticed his urine becoming dark and the stools lighter, often clay colored. The presence of polymorphic cutaneous rashes, which is described in the literature [12] as being not unusual in homologous serum jaundice,

TABLE 1.—*Periods of Incubation and Duration of Symptoms in Fourteen Patients with Jaundice*

Case	Period of Incubation, Days	Duration of Preicteric Symptoms, Days	Icteric Period, Days	Length of Stay in the Hospital Due to Hepatitis, Days
1	45	3	5	Died
2	73	3	6	Died
3	79	4	14	25
4	80	3	41	83
5	66	3	30	63
6	52	8	35	70
7	80	3	25	49
8	88	9	17	45
9	74	9	5	26
10	54	13	16	47
11	62	5	8	24
12	43	No clinical icterus	No clinical icterus	7
13	57	2	35	37
14	69	3	21	35
Average	66	5.23	19.8	42.6

occurred in only one instance in this series. Icterus appeared two to thirteen days after the onset of symptoms (table 1). Table 2 gives the symptoms and signs of the patients comprising the present series.

The length of the symptomatic stage of infectious hepatitis and homologous serum jaundice varies greatly in the literature, and it is difficult to obtain definite information. The present symptoms lasted from eight to twenty-three days, and the period of jaundice ranged between five and forty-one days (table 1).

Course.—The usual course of this disease was that of a slow convalescence following the termination of the symptomatic stage, except in 2 cases in which it was fulminating, resulting in death. If this small group of cases is a true sample of the condition as a whole, the mortality rate as evidenced by 2 fatalities (15 per cent) is much higher

12. Hawley, McFarlan and Steigman.[7b] Footnote 3*b*. Turner, Snavely and Grossman.[4c]

than that in infectious hepatitis and even in the homologous serum jaundice following injection of yellow fever vaccine. The average stay of the patients in the hospital as a result of hepatitis was forty and one-half days, and on discharge from this hospital there was no evidence of residual damage to the liver. It is the impression that these patients were usually sicker and their course more protracted than that of patients with infectious hepatitis. The increased severity of symptoms, the protracted course and the higher mortality rate in this group of patients may be explained by the following facts: 1. Each had had moderate to severe wounds. 2. All but 2 had been in combat, where the diet is notoriously poor and monotonous. 3. Their general physical condition was not so good as that of the average patient seen with infectious hepatitis or hepatitis following injection of yellow fever vaccine.

TABLE 2.—*Symptoms and Signs in Fourteen Patients with Hepatitis*

Symptoms	No. of Cases	Percentage
Malaise	14	100
Nausea and vomiting	14	100
Anorexia	14	100
Dark urine	14	100
Abdominal discomfort	13	93
Jaundice	11	78
Light to clay-colored stools	10	71
Fever	9	64
Palpable liver	8	57
Constipation	8	57
Generalized aches and pains	5	35
Chills	4	21
Pruritus	1	7
Rash	1	7
Diarrhea	1	7
Palpable spleen	0	0

Complications.—In 1 patient ascites developed seven days after the onset of symptoms, at which time the total plasma protein content was 4.5 mg. per hundred cubic centimeters of blood, with an albumin-globulin ratio of 0.83. It is questionable whether the increase of peritoneal fluid can be attributed to the low plasma protein content, as this complication is known to occur without lowering of the albumin or globulin content of the plasma and has been ascribed by Lucke [13] to endophlebitis of the veins in the portal radicles of the liver.

In 2 of the patients in this series infections of the blood stream developed. In 1 patient suffering from hemiplegia of the right side as the result of a gunshot wound of the brain there developed acute pyelonephritis and bacteremia due to Aerobacter aerogenes. These infections were treated with sulfadiazine, and the patient recovered. In the second case, in which the disease was fatal, bacteremia caused by hemolytic Staphylococcus aureus developed, which was treated by

13. Lucke, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**: 471, 1944.

means of intermittent intramuscular and continuous intravenous infusions of penicillin, following which the blood stream became sterile.

REPORT OF CASES

The 2 cases in the present series in which the disease was fatal are of sufficient interest to warrant their being reported in detail.

CASE 1.—A 28 year old white soldier (C. M.) was wounded in action in France on Aug. 1, 1944 by a high explosive shell, sustaining a compound fracture of the radius of the left arm, multiple severe penetrating wounds of the right foot, with a traumatic amputation of the fifth toe, and a mild perforating wound of the middle finger of the right hand. He was evacuated to the aid station of his battalion shortly after being wounded, and there 1 unit (250 cc.) of reconstituted lyophilized plasma was administered and preliminary treatment of the wounds was performed. From there he was rapidly evacuated back into the Zone of Communications, reaching a station hospital in England on August 4. During the evacuation, on the day following that on which the patient was wounded, a second unit of plasma was given. Definitive treatment was given at the station hospital, following which the patient was transferred to this installation on August 14 in preparation for his movement to the United States.

The patient recovered rapidly and was soon up and about on crutches but did not leave the ward. However, on September 14 the onset of fever was noted, with a rise in temperature as high as 101.8 F. accompanied with malaise, lethargy, generalized aches and pains, moderate anorexia, nausea, vomiting when he tried to eat and mild pain in the right upper abdominal quadrant. Physical examination was noncontributory at this time, and the leukocyte count was 4,850, with a normal differential count. Administration of penicillin, 20,000 units every three hours, was started because of fear of an infection under the cast despite the absence of any symptoms referable to this site. The symptoms continued unchanged until September 17, when the temperature fell to normal and the patient noticed his urine to be dark red-brown, which by laboratory examination proved to be due to the presence of bile. He was then seen to be icteric. The character of the patient's stool was not observed. Physical examination at this time revealed a patient not acutely ill and only moderately uncomfortable due to generalized malaise, lethargy and continued nausea and vomiting. The liver was palpable 2.5 cm. below the right costal margin and was moderately tender; the lower edge was rounded and firm. The spleen could not be felt. The laboratory observations at this time revealed an icterus index of 62; a total plasma protein content of 5.7 mg. per hundred cubic centimeters, with an albumin-globulin ratio of 1.3, and a blood nonprotein nitrogen content of 44.4 mg. per hundred cubic centimeters. The prothrombin time was thirteen seconds (normal control, thirteen seconds), and bile and urobilinogen were present in the urine.

The patient was put on a high protein, high carbohydrate, low fat diet, of which actually he ate extremely little. During this entire period activity was not restricted.

Icterus continued to increase, nausea and occasional vomiting were still present and pain in the right upper abdominal quadrant continued. During the evening and night of September 19 the patient became increasingly drowsy and difficult to arouse. By the morning of September 20 it was impossible to arouse him, but he became increasingly restless and difficult to handle, so that by late morning he was absolutely uncontrollable whenever he was approached to be examined, administered medicaments or fluids or for any other purpose. It became necessary

to quiet him by means of intramuscular injection of paraldehyde so that fluids could be given. Three thousand cubic centimeters of 10 per cent dextrose in sterile water plus an additional 150 Gm. of dextrose was given intravenously during the next sixteen hour period. In addition, 10 cc. of whole crude liver extract, 50 mg. of thiamine hydrochloride, 40 mg. of vitamin K, 100 mg. of ascorbic acid and 10 mg. of riboflavin were given intravenously. On September 20 the icterus index was 82, the blood nonprotein nitrogen content was 52.6 mg. per hundred cubic centimeters and the plasma protein content was essentially unchanged. Examination of the urine continued to show the presence of bile and urobilinogen in a dilution of 1:320.

Despite this therapy the patient continued to get worse, so that by the morning of September 21 he was deeply comatose and quiet, and Cheyne-Stokes type of respiration had commenced. He was more deeply icteric, and examination revealed his liver to be just palpable below the right costal margin in the midclavicular line. The spleen still could not be palpated. At this time the peripheral blood contained 18,650 leukocytes, 73 per cent of which were polymorphonuclear leukocytes, and a 95 per cent hemoglobin content (Sahli). The icterus index had risen to 122.8, the prothrombin time was 100 per cent of normal, the blood cholesterol content was 153.6 mg. per hundred cubic centimeters, the blood nonprotein nitrogen content was 45.6 mg., the blood urea nitrogen content was 6.9 mg. and the blood plasma protein content was still unchanged. The same therapeutic regimen as that given on the previous day was repeated. In the afternoon of September 21 the temperature, pulse rate and respiratory rate began to rise. About midnight the patient began retching and then bringing up large quantities of coffee ground vomitus which gave a positive reaction (4 plus) to the guaiac test. This continued until his death at 2:30 on the morning of September 22.

The pertinent observations at autopsy are as follows:

1. The left pleural cavity contained approximately 1,500 cc. of dark brown fluid with the sour odor of gastric contents and was similar in appearance to that found in the stomach. The posterior and lateral parietal pleura was opaque, gray and shaggy as a result of digestion of the fluid just described. Microscopic examination revealed this digestion to be antemortem in type.

The esophagus at its point of exit through the diaphragm was bulging into the left pleural cavity, and a defect in the muscularis measuring 1 cm. in diameter was seen. This defect did not appear to continue into the lumen of the esophagus, and on careful search no ulceration or slit of the esophageal mucosa could be demonstrated. Esophageal varicosities could not be demonstrated.

2. Minimal bronchopneumonia at the base of both lungs was seen grossly and microscopically. No definite pathogenic bacteria were found bacteriologically.

3. The liver weighed 900 Gm. The edges were more pointed than usual, and the capsule was dull and wrinkled. The organ felt extremely firm and fibrotic and cut with difficulty. The cut surface was void of the usual lobular markings and was mottled with yellow and green-gray areas.

Microscopically, only an extremely small portion of the hepatic cords remained in the granular debris which represented the remnants of the hepatic cells. There was little inflammatory reaction throughout the liver; only a few scattered polymorphonuclear leukocytes, an occasional focus of plasma cells and scattered macrophages laden with hemosiderin were seen. In some areas there was hemorrhage into the granular debris. The bile ducts were conspicuous, owing to the loss of hepatic parenchyma, and many of these contained bile casts in their lumens. Sudan III stain revealed a moderate amount of intracellular lipid within the macrophages, Kupffer cells and remaining hepatic cord cells. No inclusion bodies could be found.

4. The spleen weighed 175 Gm. It was soft but otherwise revealed nothing unusual grossly or microscopically.

5. The stomach contained about 500 cc. of red-brown sour-smelling contents. The mucosa was edematous and moderately red, due to engorged blood vessels. The edema and redness due to congestion was present throughout the small intestine. Pale gray stools were present in the rectum.

6. The kidneys were grossly normal and microscopically showed no evidence of a biliary nephrosis.

7. The brain showed nothing unusual grossly or in many microscopic sections taken from the cerebral cortex, cerebellum and medulla.

CASE 2.—A 30 year old white soldier was wounded in action in France on July 11, 1944, receiving a severe penetrating wound of the left buttock and a severe compound comminuted fracture of the entire upper one third of the left femur and associated destruction of the left sciatic nerve. On the first day of his injury he was given 2 units of reconstituted lyophilized human plasma and preliminary treatment of his wounds, definitive treatment taking place in a station hospital on July 12. He was gradually evacuated to England and finally reached the Seventh General Hospital on July 31, where further operative treatment of his severe fracture was done on September 1, at which time he received 500 cc. of human whole blood and 1 unit of plasma.

The patient did well, rapidly recovering his strength and feeling of well-being. He was, of course, confined to bed because of the spica cast which he wore.

On September 23 he began to have a low grade fever and slight malaise but no other symptoms. His temperature rose the following day, and slight anorexia was present but otherwise he felt well. The blood cell count on September 25 showed no leukocytosis, and no real symptoms of infection seemed to be present. The clinical picture continued unchanged until September 26, at which time the patient noted "funny feelings" in his epigastrium, increased malaise, moderate anorexia, nausea, chilliness and the fact that his urine was dark. He did not observe the character of his stools. Later in the day he was found to be slightly icteric, and the liver was found to be tender and palpable just below the right costal margin. The spleen could not be felt. He was given a high protein, high carbohydrate and low fat diet, which he could only partially eat. However, he did not vomit. Two multivitamin capsules were given with each meal. The following day, icterus was more striking and the appetite less and he vomited once after the noonday meal. By September 28 icterus was pronounced, but the temperature was normal most of the day and the patient seemed to feel much better. However, on the evening of September 29, the seventh day after the onset of this complication, he became drowsy, and by the following morning he was extremely difficult to arouse. Despite this fact he was becoming exceedingly restless, moving about in bed continually. In addition, he began to get incoherent in his speech, and by afternoon he was entirely disoriented. Physical examination at this time revealed him to be moderately icteric. Neither the liver nor the spleen was palpable. The laboratory data on the morning of September 30 were as follows: hemoglobin content, 97 per cent (Sahli); red blood cells, 4,720,000; white blood cells, 11,000, of which 85 per cent were polymorphonuclear leukocytes; icterus index, 57.9; serum bilirubin content, 9.0 mg. per hundred cubic centimeters, with a direct reaction to the van den Bergh test; total plasma protein content, 9.07 mg., with an albumin-globulin ratio of 1.36; prothrombin time, thirteen seconds (normal control, thirteen and one-half seconds); blood sugar level, 206 mg.; blood nonprotein nitrogen content, 48.5 mg., and blood urea nitrogen content, 13.8 mg. per hundred cubic centimeters. The urine was normal

except for bile and urobilinogen present in a 1:640 dilution. It was not until the afternoon of September 30 that a culture of the blood taken on September 25 was found to have pathogenic growth, and this was recognized tinctorially and morphologically to be hemolytic Staph. aureus. The patient was then given 200,000 units of penicillin in a continuous intravenous infusion of 3,000 cc. of 10 per cent dextrose in water during the next fourteen hours. In addition, he was given 30,000 units of penicillin intramuscularly every two hours when the intravenous medication was not being administered. Additional therapy consisted of 10 Gm. of methionine in 500 cc. of isotonic solution of sodium chloride given intravenously and intravenous administration of 10 cc. of whole liver extract, 40 mg. of vitamin K, 50 mg. of thiamine hydrochloride, 20 mg. of riboflavin and 100 mg. of ascorbic acid.

The patient continued to get worse, being in deep coma by the morning of October 1. At this time the peripheral blood had 5,540,000 red blood cells, a hemoglobin content of 103 per cent (Sahli) and 20,750 leukocytes, of which 89 per cent were polymorphonuclear leukocytes. The icterus index had risen to 105, with a serum bilirubin content of 24.8 mg. per hundred cubic centimeters; the total plasma protein content was 6.8 mg. per hundred cubic centimeters, with an albumin-globulin ratio of 1.2; the prothrombin time was fourteen seconds (normal control, fourteen seconds); the blood nonprotein nitrogen content was 37 mg. per hundred cubic centimeters, and the blood urea nitrogen content was 11.8 mg. The urine still contained bile and urobilinogen; no tyrosine or leucine crystals were present. Administration of all the aforementioned medicaments, including penicillin in the same dosages and routes, was repeated. Cheyne-Stokes type of respiration appeared by noontime, and by early afternoon he began vomiting varying amounts of coffee ground-colored material, which gave a strongly positive reaction to the guaiac test. The patient continued in this condition, never regaining consciousness, and he died at 7:05 the morning of October 2.

The essential observations at necropsy were as follows:

1. Minimal bronchopneumonia was seen microscopically at the bases of both lungs.

2. The liver weighed 800 Gm. The capsule was thin, transparent and wrinkled. The organ had ropelike consistency and cut with decidedly increased resistance. The cut surface was mottled gray-yellow, with small diffusely scattered strands or gray, suggesting fibrous stroma, and interspersed yellow-gray areas resembling abnormal hepatic cells. The gallbladder and bile ducts were normal in appearance and contained clear gray-white mucoid bile. Microscopically, examination of the liver showed only a few scattered distorted hepatic cords remaining. The vast majority were represented by granular debris. The portal areas were infiltrated by a moderate number of polymorphonuclear leukocytes, plasma cells and lymphocytes. The capillaries were greatly engorged with blood, and in areas there appeared to be hemorrhage into the hepatic stroma. Scattered macrophages contained hemosiderin. No bile casts were present in the bile ducts. No endophlebitis could be seen. Sudan III stain revealed a moderate amount of fat within the remaining parenchymal cells and the macrophages. Inclusion bodies could not be seen.

3. The spleen weighed 230 Gm. and was soft. The capsule was taut and purple-gray. On section, the pulp was soft and purple-gray, and the usual markings were not prominent. Microscopically, the findings were those of acute splenitis.

4. The gastrointestinal tract showed an engorged edematous mucosa throughout the stomach and small intestines. This portion of the tract contained material of

a coffee ground appearance, but no point of hemorrhage could be found. The rectum contained gray formed feces.

5. The kidneys were entirely normal, as were the bone marrow and the brain.

6. The wound of the buttocks and the compound fractured femur showed no evidence of infection, and, culturally, no pathogenic bacteria were found. The culture of blood taken from the heart showed no pathogenic growth.

Comment.—These 2 cases demonstrate the importance of the onset of drowsiness and/or restlessness at any time during this disease as important prognostic signs in prediction of the future course. Irritability, disorientation, irrationality, loss of memory and vague changes in the personality are likewise indications of the onset of a more serious stage of the illness or of a relapse.

A ruptured esophagus resulting from constant vomiting and retching was described by Weiss and Mallory [14] occurring in a patient who drank excessively. The finding of gastric contents in the pleural cavity of the patient in case 1 is probably an example of a ruptured esophagus by the same mechanism, despite the fact that the actual mucosal tear could not be demonstrated at autopsy.

LABORATORY OBSERVATIONS

The laboratory tests found most useful in the early diagnosis of this disease were the icterus index or test for serum bilirubin, the latter being the most delicate and accurate test, and the examination of the urine for bile and urobilinogen. These tests were also the most important ones in following the course of the illness. The level of the serum bilirubin was of great aid in determining when the patient should first be allowed out of bed and how much activity he should be permitted. Patients seemed to do best if activity was definitely restricted until the serum bilirubin level was down to 2 mg. per hundred cubic centimeters; if activity was allowed before this time, a rise in the level of the serum bilirubin of 1 to 2 mg. per hundred cubic centimeters could be demonstrated, and in 1 case mild clinical symptoms developed.

The determination of the total plasma protein content, the albumin and globulin levels and the prothrombin time was likewise valuable in following the course of these patients. There was a slight to moderate fall of the plasma protein content in all cases in which sufficient data could be collected, and in 1 case the level fell to 4.5 mg. per hundred cubic centimeters, and the patient clinically exhibited signs of ascites. In most patients there was a slight fall in the plasma prothrombin level, but in all it returned to normal limits without requiring the use of vitamin K. In the 2 fatal cases, vitamin K was administered paren-

14. Weiss, S., and Mallory, G. K.: Lesions of the Cardiac Orifice of the Stomach Produced by Vomiting, J. A. M. A. **98**: 1943 (April 16) 1932.

terally and no definite increase in the prothrombin time occurred. In no cases were the blood sugar levels unusual, except for the second fatal one, in which the initial blood sugar level was elevated to 206 mg. per hundred cubic centimeters. The blood picture was similar to that seen in infectious hepatitis, namely, a normal leukocyte level accompanied frequently with a lymphocytosis and the presence of atypical lymphocytes which are not unlike the cells in infectious mononucleosis but distinguishable from them. In the 2 fatal cases a leukocytosis developed terminally, with an increase in the polymorphonuclear elements. Table 3 gives the details of the laboratory observations.

The hippuric acid excretion test for hepatic function was not felt to be a reliable one for following the course of the disease, as its results are so dependent on normal urinary excretion. It was demonstrated by Neefe and others,[15] and confirmed in this series, that early in the course of the disease there is frequently oliguria, and during the convalescent period there may be great variations in the intake and output of fluid, which are not predictable. On many days, the output will exceed the intake, whereas at other times the output will be less than half the fluid consumed. However, as the convalescent period approaches its termination, the ratio of intake to output of fluid becomes that of a normal person, and the hippuric acid excretion test becomes of considerable aid in the estimation of residual hepatic damage. In only 1 patient was the excretion below normal standards at the time of his discharge from the hospital, which was necessitated by circumstances beyond control. An increased serum bilirubin level likewise indicated residual hepatic damage at that time.

Bacteremia developed in 2 patients in this series, which may be an indication of increased susceptibility to infections in the blood stream in this disease.

TREATMENT

The treatment of hepatitis due to homologous serum jaundice is the same as that of infectious hepatitis. High protein, high carbohydrate and low fat diet is the basis of therapy. The diet was supplemented with at least 1 quart (1,000 cc.) of powdered skim milk a day, this being made up in triple strength so that it afforded 72 Gm. of extra protein daily, with its accompanying high methionine content. The milk can be made more palatable by the use of malt, vanilla and other similiar ingredients. Sweetened fruit juice and hard candy in large quantities were given to these patients. Extra vitamins were given in all cases, with a special emphasis on the vitamin B complex. Casein digest administered orally as well as methionine administered intra-

15. Neefe, J. R.; Miller, T. G., and Chornock, F. W: Homologous Serum Jaundice: Review of the Literature and Report of a Case, Am. J. M. Sc. **207**: 626, 1944.

TABLE 3.—*Laboratory Data for Fourteen Patients with Hepatitis*

Case	Urine			Hemoglobin † %	White Blood Cell Count *	Differential Counts	Blood Chemistry							
	Bile	Urobilinogen *	Albumin				Nonprotein Nitrogen, Mg./100 Cc.*	Total Protein,† Mg./100 Cc.	Albumin-Globulin Content †	Prothrombin, per Cent of Normal †	Icterus Index *	Serum Bilirubin,* Mg./100 Cc.	Hippuric Acid Excretion at Discharge, Gm.	Heterophil Agglutinin
1	+	1:320	++	90	18,650	Polymorphonuclears, 73% Lymphocytes, 23%	52.6	5.7	1.0	100	122.8	....	...	...
2	+	1:640	++	97	20,250	Polymorphonuclears, 89% Lymphocytes, 11%	48.5	6.8	1.2	100	105	....	...	...
3	+	1:160	+	87	7,900	Polymorphonuclears, 44% Lymphocytes, 49% few atypical	30	5.0	1.1	60	46	10.3	3.9	...
4	+	1:40	++	84	9,350	Polymorphonuclears, 70% Lymphocytes, 24%	34	4.5	0.83	80	115	30.5	3.8	1:256
5	+	1:40	++	95	8,100	Polymorphonuclears, 39% Lymphocytes, 50% few atypical	31	5.7	1.1,	80	54	9.3	5.0	Normal
6	+	1:20	+	92	9,450	Polymorphonuclears, 37% Lymphocytes, 40% few atypical	29	5.9	1.1	76	130	37.5	4.8	Normal
7	+	1:80	+	90	8,950	Polymorphonuclears, 53% Lymphocytes, 38%	33	5.7	1.8	100	51	9.4	4.0	Normal
8	+	1:20	0	80	12,300	Polymorphonuclears, 53% Lymphocytes, 41%	35	5.5	1.1	100	53	14.4	3.7	Normal
9	+	1:320	+	85	12,940	Polymorphonuclears, 50% Lymphocytes, 42%	30	5.9	1.2	100	....	1.8	3.7	Normal
10	+	1:80	0	85	10,200	Polymorphonuclears, 37% Lymphocytes, 54% few atypical	....	6.3	1.8	100	....	11.3	3.0	
11	+	1:80	0	92	7,500	Polymorphonuclears, 45% Lymphocytes, 46%	33	5.7	1.36	90	....	4.6	4.1	1:64
12	+	1:20	0	87	11,900	Polymorphonuclears, 72% Lymphocytes, 22%	....	...	...	...	....	1.3	5.1	
13	+	1:40	++	76	11,600	Polymorphonuclears, 44% Lymphocytes, 44%	28	6.2	1.0	100	....	10.9	3.2	Normal
14	+	1:10	0	..	.....	.....	....	...	...	100	....	2.7	4.1	Normal

* Highest significant value. † Lowest significant value.

venously was used in a few cases, but it was not possible to draw any conclusions as to their efficacy. During the acute stages of the disease when nausea and vomiting were present, liver, plasma and intravenous injection of dextrose were used to supplement the insufficient diet. Tincture of belladonna or atropine given before meals during the acute stage seemed to be helpful in relieving the aversion to food and the nausea caused by it.

COMMENT

The main clinical points of differences between homologous serum hepatitis and infectious hepatitis are (1) period of incubation, (2) mode of spread and (3) severity. The period of incubation in the majority of cases of homologous serum hepatitis ranges between sixty and ninety days, whereas infectious hepatitis has a somewhat shorter period of incubation, averaging about thirty days. Homologous serum hepatitis is spread by the parenteral injection of human blood or its products by means of transfusions, convalescent serums, vaccines and contaminated syringes. The mode of spread of infectious hepatitis is still not completely known, but there is evidence that it may be transmitted by means of air-borne droplets and ingestion of material contaminated by the virus, namely, food and water. The severity of homologous serum hepatitis, as evidenced by the mortality rate in this series of cases and of the epidemic following injection of yellow fever vaccine,[16] is considerably greater than that seen in infectious hepatitis.

The pathologic changes of these two diseases are indistinguishable, as shown by Dible and others [17] by means of biopsies of material aspirated from the liver performed during various stages of the clinical courses. The clinical picture itself likewise has few distinguishing features to aid in differentiation of these entities.

The reasons for considering jaundice in these cases as being due to homologous serum, rather than being merely infectious hepatitis, are as follows: First, during the period in which these cases were being discovered in the surgical service, cases of infectious hepatitis in the medical service were infrequent. Similarly, cases of infectious hepatitis were not common in other hospitals during this period. Secondly, all these patients had been in a hospital at least six weeks, so that the only contact which they could have had with infectious hepatitis would have been with personnel of the hospital. Ten of the patients were in the hospital in which the onset of hepatitis occurred for over thirty days (table 4). Thirdly, it is known to be unusual for infectious hepatitis to develop in patients while hospitalized for another disease when the

16. Lucke.[18] Footnote 4 *a*.

17. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis; Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, Lancet **2**:402, 1943.

stay in hospital is longer than the period of incubation of infectious hepatitis. Fourthly, all the patients in whom hepatitis developed during this period were in the surgical service and had had plasma and often blood administered from forty-three to eighty-eight days before.

In view of the huge amount of plasma, serum and whole blood being used during both war and peace, the resulting cases of hepatitis of the homologous serum type may be numerous enough to be of considerable importance, as were the cases resulting from the previously used yellow fever vaccine which contained a human serum component. Even if large numbers of these cases are not encountered, enough will occur so that it is essential for the disease to be recognized and treated as such at the earliest possible time.

Since this type of hepatitis may occur in extremely mild form and even without jaundice, it is important that all physicians be on the alert to recognize it, so that all factors which may cause an otherwise mild or subclinical form of the disease to become a severe one may be avoided.

TABLE 4.—*Length of Stay in Hospital in Which Onset of Hepatitis Occurred*

Stay in the Hospital, Days	No. of Patients
Less than 20	3
21 to 30	1
31 to 48	2
More than 48	8

The onset of symptoms in this disease does not always herald its future course, and in many with a mild insidious onset severe and prolonged symptoms develop. In the 2 fatal cases in this series the patients had mild symptoms during its inception, but soon they became seriously ill and the course was fulminating. Therefore, it is important not only that the disease in these cases be recognized early and in its mildest forms but that it receive vigorous treatment.

Many of the patients in whom hepatitis of this type developed were either ready to be evacuated to the Zone of the Interior or in need of secondary definitive surgical treatment. Neither evacuation nor surgical treatment should be allowed during this disease. These patients should not receive either oral or intravenous administration of barbiturates during the active stage of the disease, nor should they be subjected to anesthesia by inhalation of ether until complete recovery has taken place. Detoxification of most barbiturates takes place in the liver, and in the presence of diffuse damage of this organ barbiturate poisoning may occur when otherwise nontoxic doses of these drugs are used. Ether is a hepatotoxic agent, and its use is dangerous when the liver is acutely damaged. The danger of surgical intervention in patients with hepatitis lies not only in the deleterious effects of preoperative

medication and anesthesia but in the physiologic effects of surgical trauma as well. The role of the liver in the storage and synthesis of vitamins, blood clotting and general nutrition and their relation to the healing process makes any operation during the course of hepatitis inadvisable. Thus mild and often previously unrecognized hepatitis may be made considerably worse by operative procedures, and even a fatal outcome may result. Two of the patients in this series had operations postponed until the recovery from hepatitis was complete. As mentioned before, many of these patients were ready to be evacuated to the Zone of the Interior. Six of the 14 patients observed were ready to be sent to the United States at the time of the onset of their illness. Two had already been started on this evacuation when their disease was recognized; of these, 1 had been made worse by a short journey of 35 miles (56 Km.) as judged by clinical and laboratory observations; the other had had the onset of his symptoms three weeks preceding movement to this hospital from France, and the journey seemed to have no effect on the liver as far as symptoms were concerned. Laboratory data on this patient were inadequate prior to entry to this hospital. Therefore, since travel may aggravate the disease or precipitate a relapse, it is our opinion that patients should not be transported until recovery has taken place. In addition, nausea, vomiting and retching as a result of seasickness or airsickness occurring en route might be harmful.

The problem as to the infectivity of these patients is as yet unanswered. If the nasopharyngeal secretions are actually infectious, as the experiments on transmission of Findlay and Martin [3a] would indicate, the spread of this disease to personnel and other patients of the ward would be possible. The spread by means of syringes used in routine laboratory work may occur. It has not yet been clearly demonstrated whether the agent causing the disease can be transmitted by the feces. There has been no known secondary spread of the disease in our series.

SUMMARY

Fourteen cases of hepatitis of the homologous serum type, following the administration of plasma and blood forty-three to eighty-eight days before the onset of symptoms, are briefly described and discussed. The fact that this disease may become of great importance at this time when tremendous quantities of human blood and its products are being given therapeutically is brought to the general attention of physicians, and the importance of recognizing this entity and treating it vigorously is discussed.

Two fatal cases, with the observations at necropsy, are described in detail.

Sixty-Sixth Street and York Avenue, New York.

INTRATRACHEAL PENICILLIN THERAPY IN SUPPURATIVE BRONCHIECTASIS

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NEW YORK

THE SURGICAL removal of one or more lobes of the lungs is now the accepted treatment for chronic suppurative bronchiectasis. About half the patients who suffer from this dreadful ailment are unable to undergo operation, however, because their lesions are too extensive or because they are poor surgical risks. I have sought to determine whether local penicillin therapy would help control the infectious element in the disease and thus reduce the amount of sputum in the nonsurgical and surgical patients. It was not anticipated that the drug would in any way affect the anatomic deformity of the bronchial tree.

A 62 year old dentist with bronchiectasis of the lower lobe of the left lung presented himself at the Mount Sinai Hospital in June 1944 (case 1). His illness started two and one-half years earlier with suppurative bronchopneumonia, and, after a continual febrile course for eighteen months, he had been sent to Arizona. He remained there for one year, without change in his symptoms. He coughed with little interruption and expectorated fetid, purulent sputum, the amount of which measured 120 to 180 cc. daily. Then he had a hemoptysis of 500 cc. and was returned East for further therapy, possibly lobectomy. Here, the diagnosis of saccular bronchiectasis in a shrunken lower lobe of the left lung was confirmed by bronchoscopy and bronchography. His blood pressure was 216 systolic and 110 diastolic, and his electrocardiogram showed evidence of myocardial damage. He was considered a poor risk for lobectomy, and penicillin therapy was decided on.

In order to bring the highest possible concentration of the drug to the affected bronchi, local therapy was combined with intramuscular injections. Intrabronchial instillations were favored, rather than inhalation of a nebulized mist, because of the notable induration and shrinkage of the diseased lobe. It was felt that the mist would tend to enter the bronchi of the normally respiring pulmonary areas and that lesser amounts would gain access to the indurated lobe with its impaired ventilatory efficiency. On the other hand, bronchography had already shown that the sacculations could be filled by instillation.

The patient was given 15,000 units of penicillin sodium intramuscularly every three hours. By the third day the sputum decreased in quantity to 30 cc. in twenty-four hours. On this day, after preliminary postural drainage, 10,000 units of penicillin sodium dissolved in 100 cc. of isotonic solution of sodium chloride was instilled into the lower lobe of the left lung by means of a soft rubber catheter. The tube was introduced under fluoroscopic control after the larynx and trachea

The penicillin used in this study was supplied through the courtesy of Schenley Laboratories, Inc.

From the Service for Thoracic Diseases and the Medical Department of the Mount Sinai Hospital.

were cocainized. The patient was then placed in bed in a sitting position, leaning toward the left, and was cautioned against coughing during the next two hours. There were no signs of bronchial irritation following the treatment. The instillations were given daily, and the dose was increased to 25,000 units in the same amount of isotonic solution of sodium chloride. After the second intrabronchial instillation, on the seventh day of the intramuscular course, there was no more sputum

The patient lost his cough and slept undisturbed for the first time in two and one-half years. Administration of the drug was continued by both routes for five days, and then the intramuscular injections were stopped. The instillations were continued to a total of eleven. The patient was given, in all, intramuscular injections for four days, combined therapy for five and intrabronchial treatment alone for six days. He received a total of 1,060,000 units of penicillin, 260,000 units of which was given intrabronchially. He left the hospital, without symptoms, after a three weeks' stay and has remained under observation since.[1]

This surprisingly favorable immediate result prompted further trial of the method.

MATERIAL

During 1944 and 1945, 13 adults with chronic suppurative bronchiectasis and 1 child with suppurative pneumonia and early bronchiectasis were treated. Three of these patients were judged suitable for

TABLE 1.—*History and Extent of Involvement*

Case	Age, Yr.	Sex	Duration of Symptoms Yr.	Lobes Involved with Bronchiectasis
1 (M. J.)	63	Male	2½	Lower lobe of left lung
2 (M. S.)	30	Female	28	Right lung, lower and middle lobes; left lung, lower lobe
3 (J. N.)	63	Male	25	Lower lobes of both lungs
4 (T. M.)	26	Female	24	Both lobes of left lung
5 (G. B.)	37	Male	2½	Lower lobe of left lung
6 (A. E.)	33	Female	16	Lower and middle lobes of right lung
7 (J. T.)	50	Male	16	Lower and middle lobes of right lung
8 (H. H.)	63	Female	30	Right lung, all lobes; left lung, upper lobe
9 (M. S.)	52	Male	6	Lower lobes of both lungs
10 (J. I.)	20	Male	15	Right lung; lower and middle lobes; left lung, lower lobe
11 (B. R.)	17	Female	7	Right lung, all lobes; left lung, upper lobe
12 (J. G.)	25	Male	17	Right lung, lower and middle lobes; left lung, both lobes
13 (S. K.)	50	Male	18	Lower lobe of left lung

lobectomy. Two had lobectomy after preliminary penicillin therapy, with a definite cure. One is still considering the operation. In all instances the extent of the disease was determined by bronchography, and in 10 patients the disease was multilobar. The main lesions were in the bronchi of the lower lobes of both lungs and of the middle lobe of the right lung. Eleven patients had extensive sacculations in the affected lobes. Two had cylindric dilatations. Bronchography revealed shrinkage of the involved lobes in all patients. The symptoms had endured ten or more years in 9 patients (table 1). All patients were

1. Siltzbach, L. E.: Penicillin Therapy in a Case of Chronic Suppurative Bronchiectasis, J. Mt. Sinai Hosp. **12**:825 (July-Aug.) 1945.

expectorating at least 40 cc. of purulent sputum daily, and in 7 cases the sputum was decidedly fetid.

METHOD OF TREATMENT

After the first 2 patients were treated, the technic was changed from intrabronchial to intratracheal instillations. The drug was introduced into the trachea through a Mosher laryngeal life saver—a metal tube—and was directed to the desired lobe by positioning of the patient. The individual dose of penicillin was increased to 100,000 units, and the diluent of isotonic solution of sodium chloride was reduced to 20 cc. The lesser volume of fluid was better borne.

The patients received a course of seven to fifteen instillations over a period of eleven to eighteen days. Treatments were given daily or on alternate days. The instillation therapy was not instituted until the patient's course had become afebrile. Ten of the patients also received 15,000 to 30,000 units of penicillin intramuscularly every three hours, and in 3 instances the injections were continued along with the instillations. Four patients were treated with inhalations of nebulized penicillin in doses of 50,000 units per cubic centimeter four times daily, three before the instillations were begun and one after they were completed. Five had sulfonamide drugs orally before instillations were initiated. In general, instillations were begun when no further beneficial effect was obtained with the other methods of treatment.

SIDE EFFECTS

Half the patients had a moderate rise in temperature about six hours after some instillations. The fever generally lasted for a few hours and, with 1 exception (case 13), was not associated with roentgenologic evidence of extension of the infiltrations. In the exceptional case an extension was noted in the region of the old lesion after the seventh instillation and the treatment was discontinued. After six days the roentgenogram of the chest showed resorption of the infiltration, with a return to the previous status. It is of interest that shortly after this episode there developed in the patient an urticarial rash, which also disappeared within a few days. In another patient a transient rash and eosinophilia developed, and in still another there developed eosinophilia without any other allergic manifestation.

LEVELS OF PENICILLIN IN THE SPUTUM

In order to learn whether the instilled penicillin was being retained in the bronchial tree for significant periods, the concentrations of penicillin in the sputum were determined at intervals of one to five days after an instillation. Thirty-seven specimens were analyzed. Of eighteen specimens which were obtained twenty-four hours after instillation, sixteen revealed concentrations of 0.12 to 100 units per cubic centimeter of sputum. Twelve of these specimens had more than 1.0 unit per cubic centimeter. Eight out of twelve specimens obtained after forty-eight hours contained penicillin, the highest concentration being 10 units per cubic centimeter. Even after seventy-two hours four out of five

specimens contained the drug, one of them containing 5.5 units per cubic centimeter. Two specimens, obtained four and five days after an instillation, did not contain the drug. Penicillin administered intramuscularly could not be recovered from the sputum even when the doses by this route were as large as 400,000 units a day.

PENICILLIN IN EXCISED PULMONARY TISSUE

In 1 case there was an opportunity to ascertain whether the instilled drug was reaching the diseased portions of the lung. Forty-eight hours before lobectomy, 100,000 units of penicillin dissolved in 20 cc. of isotonic solution of sodium chloride was introduced intratracheally into the affected lobe. Intramuscular injections of penicillin were withheld for three hours preoperatively. A sample of blood drawn while the lobe was being removed contained no penicillin. On the other hand, several pieces of pulmonary tissue with diseased bronchi contained a concentration of 0.4 unit of penicillin per gram of pulmonary substance.

BLOOD LEVELS AFTER INSTILLATIONS

It was to be anticipated that following the intratracheal instillation of large doses of penicillin its presence would be detectable in the blood. In all specimens drawn within four hours, concentrations of at least 0.13 unit per cubic centimeter of serum were found. Peak levels occurred twenty to thirty minutes after the instillations. The highest was 4.0 units per cubic centimeter of serum thirty minutes after instillation of 100,000 units in 20 cc. of isotonic solution of sodium chloride. The concentrations of penicillin in the blood and sputum roughly paralleled the size of the dose instilled.

CHANGES IN CHARACTER OF SPUTUM WITH TREATMENT

The sputum changed in character after the first three or four instillations. In the 7 cases with fetid sputum the odor was abolished. In most instances the sputum became less purulent and more mucoid. Its bacterial flora also was altered. In general, the gram-positive organisms, such as Streptococcus viridans, Staphylococcus aureus and Staphylococcus albus, diminished or disappeared, and for the most part only gram-negative organisms—Escherichia coli and Hemophilus influenzae—could be cultured. In 1 case a bronchoscopic specimen obtained twenty-four hours after an instillation was sterile on aerobic and anaerobic culture. The usual respiratory flora tended to recur in about one week after the instillations were terminated. No relation appeared between the response to treatment and the sensitivity to penicillin of the predominating organisms or the disappearance of any single organism from the sputum.

CRITERIA

Changes in the average volume of sputum in twenty-four hours were measured. These changes are a crude criterion, but one could not utilize alterations in the roentgenologic shadows of the lungs, since their pattern is usually set in patients with chronic suppurative bronchiectasis.

A pretreatment base line was established by measuring the volume of sputum in twenty-four hours for about one week while the patient practiced postural drainage. Three days were allowed for the drug to take effect. Then the daily volume of the sputum for the remaining period of therapy was averaged.

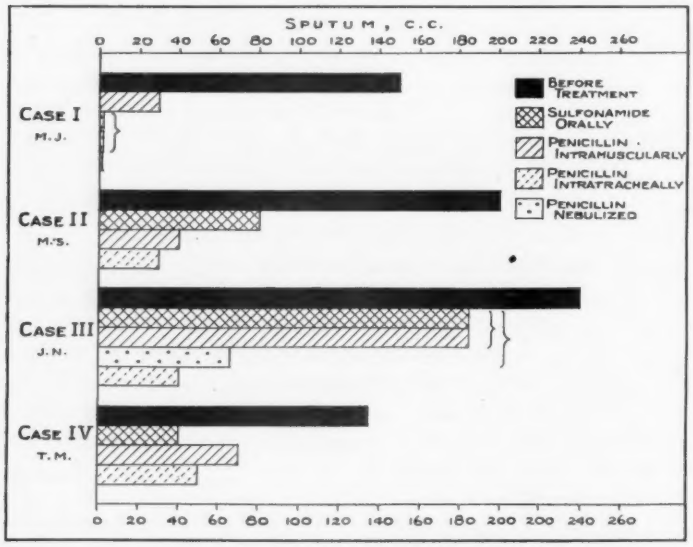

Fig. 1 (cases 1 to 4).—Average volume of sputum in twenty-four hours under specified therapy administered successively. Brackets indicate combined therapy. The lowest bar in case 1 represents the volume of sputum under intratracheal therapy alone.

A patient's response to therapy was considered poor if there was a reduction in the amount of sputum of less than 50 per cent, fair if the decrease was 50 to 80 per cent, good if the decrease was above 80 per cent and excellent if expectoration ceased. The immediate results of treatment are shown in figures 1, 2 and 3. The late results, after six to twenty-one months' follow-up observation, are given in table 2.

SUMMARIES OF CASES

CASE 1.—The course of the disease in the 62 year old dentist has been described. Before treatment he expectorated 150 cc. of foul purulent sputum daily (fig. 1).

The drop to 30 cc. with intramuscular therapy and the disappearance of his symptoms after combined and then local therapy alone are shown. He has been working for twenty-one months and has had no recurrence of expectoration despite three episodes of coryza.

CASE 2.—The patient was a 30 year old woman in whom bronchiectasis had developed when she was 2 years old. The disease followed suppurative pneumonia complicating measles and pertussis. She had repeated attacks of pneumonia thereafter, and for the last fifteen years she had been confined to her home and had taken her meals in a room apart from her family because of the fetid sputum. The bronchogram showed that the lower lobes of both lungs and the middle lobe of the right lung were involved. Large sacculations were present. The patient was expectorating about 200 cc. of extremely fetid sputum (fig. 1). A sixteen day course of sulfadiazine reduced the amount of sputum to about 80 cc., but this remained fetid and purulent. Intramuscular injections of penicillin—15,000 units every three hours for one week—further reduced the amount of sputum to 40 cc. This also was purulent but was less odorous.

Fourteen daily intratracheal instillations of 50,000 units of penicillin dissolved in 50 cc of isotonic solution of sodium chloride were given bilaterally. The amount of sputum dropped to 30 cc., and for the first time the odor was abolished. The patient has been observed for seventeen months. Except for a rise in the volume of sputum to 60 and 90 cc. respectively following attacks of coryza one month and two months after treatment, the patient's sputum has stayed below 30 cc. in amount and has never since had an odor.

This was considered a good immediate result, and it was well maintained.

CASE 3.—The patient was a 63 year old man who was extremely ill when admitted to the hospital. He had fever and was much too weak for instillations. His illness dated back twenty-five years and had grown considerably worse in the last year and a half. His sputum was fetid and amounted to 240 cc. daily. A bronchogram made earlier showed extensive saccular bronchiectasis in the lower lobes of both lungs. There had been recent pneumonic extensions into the upper lobes. As figure 1 shows, he got relatively little benefit from combined intramuscular injections of penicillin and sulfonamide drugs but did well when there was added 50,000 units per cubic centimeter of nebulized penicillin four times a day.

The quantity of sputum dropped from 185 cc. to 65 cc. His fever subsided, and he felt stronger. The sputum was still purulent and odorous, and he was therefore given eight intratracheal instillations of 100,000 units in 20 cc. of isotonic solution of sodium chloride over a period of thirteen days. Under this therapy, the sputum lost its odor and became mucoid and the quantity decreased to 40 cc. a day. The patient was discharged much improved, and he returned to part time work. After one month, however, the sputum was again foul and amounted to 120 cc. daily. He entered his local hospital and died four months after the penicillin treatment had been terminated. The cause of death was failure of the right side of the heart and generalized amyloidosis.

In this instance there was a good immediate result, but recurrence took place within two months.

CASE 4.—A woman of 26 years was admitted for lobectomy. The lower lobe of her left lung was the seat of extensive sacculations. The bronchi of the lingula were slightly involved. She had a sizable reduction in amount of sputum during sulfonamide therapy (fig. 1), but within one week the sputum rose again to its original volume. With the patient under intramuscular penicillin therapy the level of sputum dropped to a daily average of 70 cc., and a further decrease to 50 cc.

followed intratracheal instillations. She left the hospital, and for the first two weeks the sputum was mucoid and odorless and the volume measured but 10 cc. Within a month, however, it became purulent and fetid and the amount climbed to 75 cc Another series of instillations reduced the volume by half, and then lobectomy with lingulectomy was performed, with cure. The excised lobe showed evidence of persisting bronchial infection.

The immediate response was fair, but there was a recurrence one month afterward.

Case 5.—A 32 year old man was admitted for lobectomy. He had saccular bronchiectasis of the lower lobe of the left lung, dating back two and a half years, and was expectorating on the average of 100 cc. of fetid sputum (fig. 2), He was

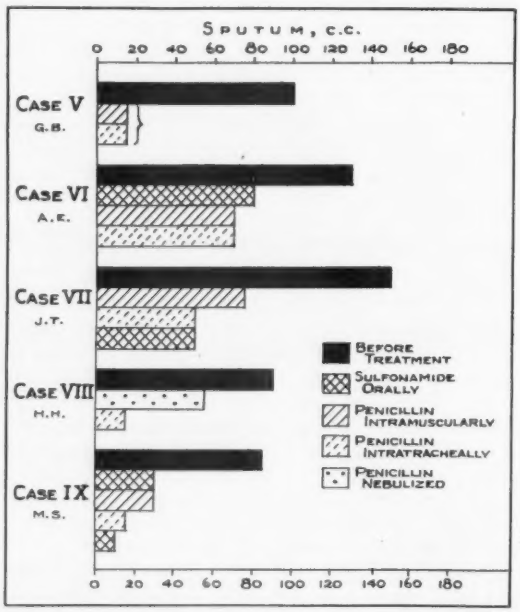

Fig. 2 (cases 5 to 9).—Average volume of sputum in twenty-four hours under specified therapy administered successively.

submitted to bronchoscopy, and the bronchoscopist reported as follows: "A large quantity of foul, sanguinous, purulent material wells up from all branches of the lower lobe of the left lung. The mucosa is inflamed and bleeds easily." In preparation for lobectomy, the patient was given ten daily intratracheal instillations of 100,000 units of penicillin combined with 15,000 units every three hours intramuscularly.

After the sixth instillation there was no longer any cough or expectoration. Twenty-four hours after the ninth instillation bronchoscopy was performed again, and the bronchoscopist's findings were "small particles of nonodorous secretion clinging to the wall of the bronchus of the lower lobe of the left lung. There was no appearance of pus with cough. The mucous membrane was paler and did not bleed. This was a dramatic resolution of a suppurative process. There was

no odor and practically no secretion." Aerobic and anaerobic culture of the bronchoscopic secretions failed to reveal any growth. The patient remained asymptomatic, and the lobectomy was postponed. However, after a month the cough and expectoration returned, and the volume of sputum, again foul and purulent, measured 75 cc. The patient was given three more intrabronchial instillations in preparation for lobectomy, and by the day before the operation the level of sputum had decreased to 15 cc. The bronchi of the excised lobe contained little secretion. The operation resulted in a definitive cure.

Here was another excellent immediate result with a recurrence after one month followed by a satisfactory preoperative response.

CASE 6.—A woman of 33, with two lobes involved, had a drop in the level of sputum of less than 50 per cent after treatment (fig. 2). She suffered exacerbation of her symptoms, with spread of the disease three weeks after her discharge from the hospital. She is still considering surgical treatment.

The immediate and the late results were poor.

CASE 7.—The patient in this case had a fair immediate result, the amount of sputum dropping from 150 cc. to 50 cc. (fig. 2). Most of the decline occurred while the patient was receiving 100,000 units intramuscularly every six hours for nineteen days. Despite weekly intratracheal instillations of penicillin in the outpatient department, the volume of sputum returned almost to its original level after six weeks—a poor result.

CASE 8.—A 63 year old woman had symptoms for fifty years, with several acute exacerbations in the last year. On admission to the hospital her temperature was 102 F. Since she was too ill for intratracheal therapy, a nebulum of 50,000 units of penicillin dissolved in 1 cc. of isotonic solution of sodium chloride was given four times daily. During the first week the volume of sputum dropped from 90 cc. to 55 cc. (fig. 2). It remained at about that level during the second week of the inhalations. Her temperature became normal, and her strength increased. After eleven intratracheal instillations of 100,000 units of penicillin in 20 cc. of isotonic solution of sodium chloride, the amount of sputum decreased to 15 cc and it became mucoid. The patient has been observed for eleven months, and the amounts of sputum have remained at the same level.

The immediate and late results were good.

CASE 9.—The patient in this case also had a good immediate result—a drop in the level of sputum from 85 cc. daily to 15 cc. at the end of intratracheal treatment (fig. 2) He has been observed for eighteen months, and his daily volume of sputum has not exceeded 30 cc.—a fair late result.

CASES 10 and 11.—The patients in these cases had fair immediate results (fig. 3), which have been maintained for fifteen and eight months respectively.

CASES 12 and 13.—Nothing was gained from the therapy (fig. 3).

CASE 14.—This case is of particular interest. The patient was a 9 year old child who became ill with pertussis in the beginning of February 1945. Several weeks later she was found to have suppurative pneumonia and was admitted to a hospital for contagious diseases. The roentgenogram of her chest showed consolidation and atelectasis of the lower and middle lobes of the right lung. She was submitted to bronchoscopy twice, and large quantities of odorless pus were aspirated from the right bronchial tree. She was given a total of 2,640,000 units of penicillin intramuscularly and also a course of sulfonamide drugs during the next month, but without improvement.

In the ninth week of her illness she was transferred to the Mount Sinai Hospital. She still had fever and expectorated about 45 cc. of purulent sputum. On her admission to the hospital roentgenograms of her chest, taken on March 31, 1945, showed atelectasis of the lower and middle lobes of the right lung. Bronchoscopy was performed on April 6, and large quantities of odorless pus were aspirated from the bronchi of the lower and middle lobes of the right lung. Penicillin was given intramuscularly in doses of 20,000 units every three hours—altogether, 3,500,000 units over a twenty-three day period.

The fever subsided, and the amount of sputum dropped to about 15 cc. but was still purulent. On May 10 bronchoscopy was performed again and thick pus was aspirated from the same bronchi, but the secretions were not so profuse as they had been one month earlier. The physical signs of atelectasis persisted,

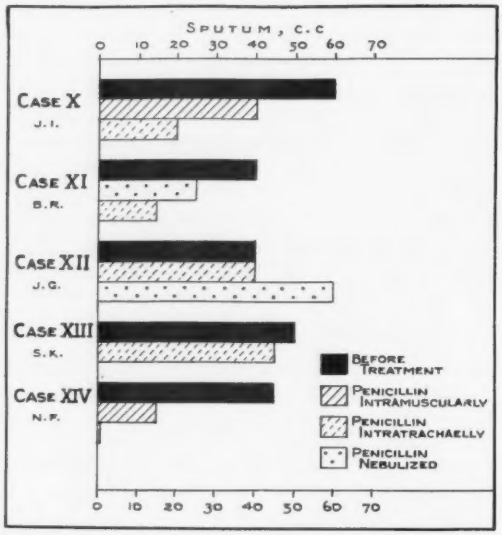

Fig. 3 (cases 10 to 14).—Average volume of sputum in twenty-four hours under specified therapy administered successively. The lowest bar in case 14 represents the volume of sputum under intratracheal therapy.

and a roentgenogram of the chest made one week after bronchscopy showed, on May 17, 1945 (fig. 4 *A*), that the lobes were still collapsed. The intramuscular injections of penicillin were resumed after bronchoscopy.

Because of the persistent atelectasis, a course of intratracheal penicillin therapy was started on May 22, 1946. By June 5 the patient had been given five instillations of 50,000 units in 10 cc. of isotonic solution of sodium chloride. After the third instillation the cough and expectoration disappeared.

A roentgenogram made on the day of the last instillation showed, for the first time in more than three months, partial reexpansion of the lobes (fig. 4 *B*). Eleven days later there was practically complete aeration of the involved lobes (fig. 4 *C*). Three months later a bronchogram of the lower and middle lobes of the right lung showed that she had not entirely escaped the sequelae of the suppurative pneumonia and atelectasis in spite of the normal-appearing roentgeno-

gram of the chest. There was slight cylindric dilatation of the anterolateral branch of the bronchus of the lower lobe of the right lung. She has now been observed for thirteen months, and there has been no recurrence of cough or expectoration in spite of two attacks of coryza.

RESULTS OF TREATMENT

Immediate results were considered excellent in 2 patients, both of whom had their disease for only two and one half years; good in 4 patients; fair in 4, and poor in 3. Thus 10 out of 13 patients experienced a drop in volume of sputum of 50 per cent or more immediately after treatment. Four of them had a recurrence of symptoms within two months. The 3 with poor immediate results remained in this

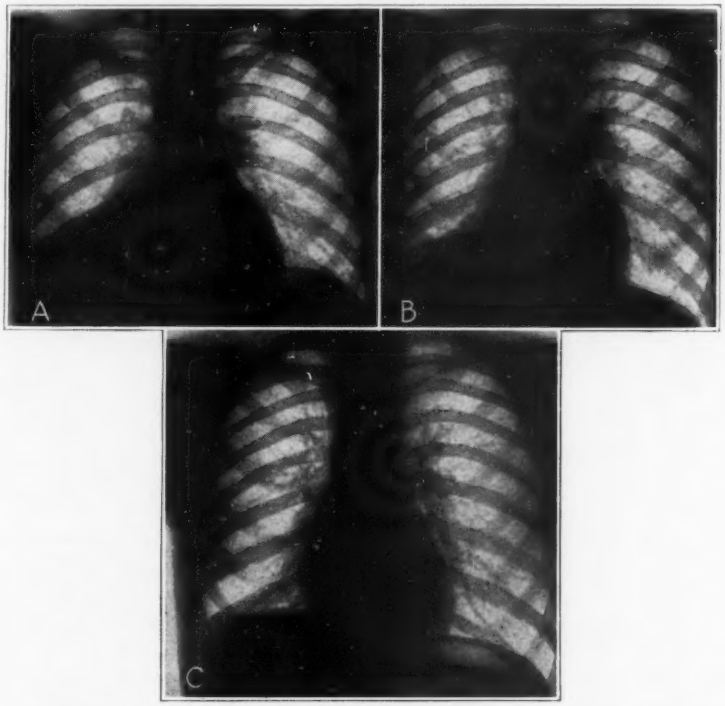

Fig. 4.—Roentgenograms of the chest of a 9 year old child with suppurative pneumonia and atelectasis following pertussis. *A*, roentgenogram of the chest before intratracheal penicillin therapy shows diffuse opacity in the lower field of the right lung, representing atelectasis of the lower and middle lobes. The appearance has been unchanged for more than three months. *B*, roentgenogram of the chest taken on the last day of intratracheal penicillin therapy, with beginning reexpansion of the previously unaerated lobes. *C*, eleven days later almost complete aeration of the affected lobes has occurred.

category. The later results were therefore as follows: excellent in 1, good in 2, fair in 3 and poor in 7.

It is to be remarked that of the 10 patients with a favorable immediate result the addition of intrabronchial or intratracheal administration of penicillin was accompanied in almost all by a reduction in the

TABLE 2.—*Immediate and Late Results of Treatment with Intratracheal Administration of Penicillin*

Case	No. of Instillations	Single Instillation Dosage, Units	Average 24 Hour Volume of Sputum, Cc.		Results of Treatment *		Comment
			Before Treatment	With Intratracheal Administration of Penicillin	Immediate	Late	
1	11	10,000 to 25,000	150	None	Excellent	Excellent	No recurrence after 21 mo.; completely free of cough and expectoration
2	14	50,000	200	30	Good	Good	No significant recurrence in 17 mo.; sputum, 30 cc. or less; no odor
3	8	100,000	240	40	Good	Poor	Recurrence after 2 mo. and death from failure of the right side of the heart and amyloidosis in 4 mo.
4	12	37,500 to 75,000	135	50	Fair	Poor	Recurrence after 1 mo.; lobectomy and cure
5	10	100,000	100	15	Excellent†	Poor	No sputum at end of instillations; recurrence in 1 mo., with 75 cc. of fetid and purulent sputum; preoperative instillations, with reduction to 15 cc., followed by lobectomy with cure
6	13	100,000	130	70	Poor	Poor	Exacerbation, with spread of disease in 3 wk.; no improvement for next 6 mo.; patient awaiting lobectomy
7	12	100,000	150	50	Fair	Poor	Recurrence in 6 wk.; no improvement for next year
8	11	100,000	90	15	Good	Good	No recurrence; sputum about 15 cc. for next 11 mo.
9	15	30,000 to 50,000	85	15	Good	Fair	No recurrence; sputum 30 cc. or less for next 18 mo.
10	12	50,000 to 100,000	60	20	Fair	Fair	No recurrence; sputum 25 cc. for next 15 mo.
11	10	200,000	40	15	Fair	Fair	No recurrence; sputum 15 cc. or less for next 8 mo.
12	13	200,000	40	40	Poor	Poor	Condition unimproved during the next 6 mo.
13	7	200,000	50	45	Poor	Poor	Condition unimproved during the next year

* Excellent indicates cessation of expectoration; good, reduction of sputum exceeding 80 per cent; fair, reduction of sputum 50 to 80 per cent, and poor, reduction of sputum less than 50 per cent.

† Expectoration ceased after the sixth instillation.

volume of sputum beyond that which had previously been effected by intramuscular injections of penicillin, nebulized penicillin or sulfonamide drugs. Moreover, the only 2 patients whose symptoms entirely disappeared immediately after treatment (cases 1 and 5) were both

given intratracheal and intramuscular therapy simultaneously. It may be noted further that 2 other patients with recent pneumonic spreads, who could not be given instillations initially, improved considerably with inhalations of nebulized penicillin (cases 3 and 8). Both these patients had further reductions of sputum with intratracheal instillations.

There are instances, however, in which nebulized penicillin apparently does not reach the affected portion of the bronchial tree. A recent experience with a patient not included in the present series illustrates this. The patient had suppurative saccular bronchiectasis of the middle lobe of the right lung and was being prepared for lobectomy. Bronchoscopy revealed large amounts of fetid pus pouring out of the bronchial orifice of the middle lobe of the right lung, which was considerably narrowed by swelling of the mucosa. A ten day course of nebulized penicillin, administered for fifteen minutes every hour for twelve hours daily, resulted in no change in the amount or the character of the sputum. However, five instillations of 100,000 units of penicillin dissolved in 10 cc. of isotonic solution of sodium chloride, given daily through a bronchoscope directly into the orifice of the middle lobe of the right lung, resulted in the complete disappearance of the secretions, and when the lobe was excised the dilated bronchi and their sacculations were found to be almost completely dry. At the present time some patients are being treated with a preliminary course of nebulized penicillin, and when the response is not entirely satisfactory a series of intratracheal instillations is prescribed.

The fair proportion of patients with a favorable immediate response would indicate that the combined intratracheal and intramuscular therapy may be a valuable adjunct in the preparation of patients for lobectomy. A drier and less infected bronchial tree should aid in the prevention of aspiration of pus into uninvolved pulmonary areas during and after surgical treatment. For patients not treated surgically the therapy as given holds out less, although some appear to obtain fairly lasting amelioration of symptoms. Obviously, instillations cannot be continued indefinitely. It remains to be seen by further study whether the incidence of recurrence can be lessened by prolonged administration of nebulized penicillin or by the addition of other antibiotic and chemotherapeutic agents.

The single experience with atelectasis complicating suppurative pneumonia—the forerunner of bronchiectasis—suggests that intratracheal instillations may be a useful addition to the present methods of therapy. Further trial of the method in the important area of the prevention of bronchiectasis is in progress.

SUMMARY

1. Thirteen patients with chronic suppurative bronchiectasis and 1 patient with suppurative pneumonia, atelectasis and early bronchiectasis were treated with intratracheal instillations of penicillin.

2. Ten of the 13 patients with chronic bronchiectasis had a drop of 50 per cent or more in the volume of sputum in twenty-four hours following the instillations. In each case the instillations held the volume of sputum at a lower level than could be maintained previously with the use of sulfonamide drugs, intramuscular injections of penicillin or nebulized penicillin. Three patients had no significant reduction of sputum after the instillations.

3. Recurrence of symptoms was experienced by 4 patients with a favorable immediate response. All recurrences took place within two months.

4. Intratracheal penicillin therapy appears to be a useful adjunct in the preparation of patients for lobectomy. It reduces the volume of sputum, renders it less purulent and abolishes the odor.

5. Some patients unsuitable for surgical intervention obtain fairly lasting ameliorative effects from the therapy.

6. One patient with suppurative pneumonia and atelectasis of more than three months' duration experienced immediate and lasting clearing and reexpansion of two lobes after intratracheal instillation.

1097 Madison Avenue.

News and Comment

Annual Meeting of American Psychiatric Association.—The one hundred and third annual meeting of the American Psychiatric Association will be held in New York, May 19 to 23, at the Pennsylvania Hotel. The association was founded in 1883 and is the oldest body of medical specialists in the country. It has over 3,500 members in the United States, Canada, Latin America and Europe.

The program consists in one hundred and twenty papers reporting on advances in such diverse fields as child psychiatry, brain surgery, convulsive disorders, shock therapy, alcoholism and forensic psychiatry. Leaders in the Veterans Administration will meet on Wednesday morning.

The program includes: a symposium on the treatment of the hospitalized neuropsychiatric patient; a discussion on motivation in recovery from medical and psychiatric illnesses; reports on physiologic and clinical rationale of the new brief stimulus therapy and on a study of the effect which electric shock therapy has on mental functions; a clinical evaluation of electronarcosis therapy in comparison with electroshock therapy, and the part psychiatry plays in the administration of justice. On Wednesday afternoon there will be a presentation on the recently organized nonprofit Psychiatric Foundation and its role in public education and on the role of psychiatry in the world today. On Thursday afternoon papers will be presented on the experiences and implications of psychiatry in World War II; reports will be presented on two hundred lobotomies performed on patients with diverse psychiatric conditions, and there will be reports on outpatient treatment of persons with chronic alcoholism, penicillin therapy in dementia paralytica and the use of ergotamine compounds in the treatment of simple anxiety states. On Thursday evening a round table dinner discussion will be held on the program of the United States Public Health Service for the development of training, research and community service in mental health, as well as discussions on the role of social agencies in dealing with constitutional psychopaths and the importance of psychophysiologic interrelationships.

On Friday afternoon a report will be presented on an experiment in group psychotherapy of patients for whom interpersonal difficulties in the home appeared noxious.

Further information may be procured by writing to the secretary-treasurer of the American Psychiatric Association, Dr. Leo H. Bartemeier, 3044 West Grand Boulevard, Detroit.

Book Reviews

The Diagnosis and Treatment of Pulmonary Tuberculosis. By Moses J. Stone, M.D., and Paul Dufault, M.D. Price, $3.50. Pp. 325, with 93 illustrations. Philadelphia: Lea & Febiger, 1946.

This small volume is remarkable because so much sound information on pulmonary tuberculosis has been condensed into such little space. By the elimination of illustrations, blank pages and bibliography there is only a little more than 200 pages of text; yet practically every field of pulmonary tuberculosis has been clearly, if but briefly, discussed. The authors' claim that "brevity is the byword" is obviously substantiated. Nevertheless, the work is a good textbook and not a compendium. Naturally, such condensation is not to be expected in any work meant for research workers or specialists; the authors state that it is for "students, teachers and all physicians desiring a practical knowledge of the disease." Even for the most highly trained, however, it affords a refreshing review of the important phases of tuberculosis without any "dissertations and controversies."

One of the outstanding educational features is the attempt to correlate clinical and roentgenologic observations with good illustrations of the pathologic changes. There is also a modernization of clinical methods, especially methods of physical examination, with an excellent appraisal of values. Obsolete procedures (such as measuring the Krönig isthmus) are put in the "historical museum," but the necessity of a thorough study of the human being by the taking of the history, inspection, palpation, percussion and auscultation still exists in spite of the far greater usefulness of roentgen rays, because the "x-ray may not always be available." This reviewer would also suggest that methods other than roentgenologic provide "added knowledge of the patient, which x-rays and laboratory cannot give." Differential diagnosis, various complications, methods of treatment, after-care and rehabilitation are generally well covered.

In view of the attempt to arrive at a happy medium between brevity and a mass of facts, the product must be expected to have something lacking. It is hoped that the following remarks may be considered as suggestions rather than as criticisms, and that the authors may be able to effect certain changes in future editions.

In spite of studied intentions, certain controversies are unavoidably encountered, because their elimination would emasculate any work on diseases of the chest. The views on allergy and immunity, the protection afforded by the primary infections, the question of cancer of the lung versus cancer of the bronchi and indications for the many forms of treatment are by no means closed chapters. What was meant to be eliminated, no doubt, are bygone historic differences of opinion which now add romance and make the subject attractive for the medical historians and research workers.

The differential diagnosis, although rather good, still lacks the mention of some important conditions, such as lipid pneumonia; chronic streptococcic, staphylococcic and Friedländer pneumonia; massive collapse; infarction; passive congestion from cardiac disease; atopic asthma, and malformations. There should be a paragraph on emphysema, because of its pathogenesis and its frequent presence as a diagnostic problem in diseases of the chest. The paragraphs on industrial disease do not include siderosis; the discussion on tumors might well include dermoids, fibromas, neurofibromas, mesotheliomas and tumors of the cord and body wall which encroach on the pleura or the pulmonary structures. The fifty or more other diseases are of course too uncommon to merit consideration in such a limited text.

More emphasis might well be given the complex diagnostic problem of concomitant and associated disease. In addition to diabetes, syphilis and silicosis,

cancer of the lungs, bronchiectasis, asthma and the whole gamut of diseases of the lungs could well be cited as occasionally complicating the diagnosis and treatment of tuberculosis. Furthermore, the association of mental disease and tuberculosis is almost a specialty of its own.

In the discussion of management of sanatoriums the different problems arising in the home; in private, public and veterans' hospitals, and especially in mental institutions might have been mentioned to advantage. The importance of nursing care and esthetic environment are perhaps underemphasized.

One error of calculation appears on page 203, where cases involving pneumothorax are said to be 0.4 per cent of all cases cited, whereas the figure should be about 4.5 per cent.

Regarding the "unknown cause" of psittacosis, there seems to be little doubt now that it is of virus nature.

The bibliography does not appear to contain the most representative references, but the illustrations are exceptionally well chosen, of the highest grade and are well reproduced. The format, paper, binding, print and publishing are beyond criticism.

This book is highly recommended for undergraduates as perhaps the best modern text in English for classroom work. It is also good for the book shelf of every physician.

Publicaciones del Centro de Investigaciones Tisiologicas. Edited by Prof. Roque A. Izzo, Director. Vol. IX. Buenos Aires, Argentina: Pabellon "Las Provincias," Hospital Tornu, 1945.

The ninth collection of papers of "Del Centro," under Professor Izzo's direction, contains some valuable contributions.

The first article, on the roentgenologic exploration of the hearts in a group of 23 cases of mitral stenosis in adults by Laplace, is especially good. In addition to the standard measurements, the author describes how other signs may be of great usefulness. By a discussion of the skilful application of fluoroscopy and exposures at a distance of 2 meters (teleroentgenograms) on both anterior-posterior and oblique views, the author brings out some refined methods of detecting the progressive stages of mitral stricture.

The study is divided into sections on the heart and its borders, the mediastinum and the pulmonary fields around the heart. The cardiac changes are more or less progressive in a definite order. With regard to the anterior-posterior view, the author describes first the left border of the heart. Two types ae recognizable, viz., the early type, in which the region of the pulmonary conus becomes flattened and the angle between the left ventricle and pulmonary artery obliterated (47.8 per cent of the cases), and the advanced type, with varying degrees of expansion outward from the region of the conus (52.2 per cent of his cases). The fine differentiation of the left auricular appendage (which is fixed) from the pulmonary artery (which pulsates) is intriguing but seems academic or only for the most highly skilled observer.

The right border of the heart also passes through several stages of involvement following or overlapping those on the left, characterized at first by an incursion of the left auricle into the field, eclipsing partially the upper right auricle and apparently the aortic-auricular junction. Later the right auricle enlarges, and at the same time it rotates the heart around the axis toward the left. As a consequence, there is frequently the double image originating at the aortic-auricular junction and separating downward. The elevation and lengthening of the auricular arc were present in 96 per cent of the cases studied, but the "double arc" phenomenon was present only in 26 per cent of the cases. All 23 cases showed various combinations of the described phenomena. Cossio's sign of "dancing bronchi" is mentioned, but it is probably due to "dancing" blood vessel columns.

The mediastinal phenomena are, first, the clinical phenomenon (Ortner's sign, i. e. partial paralysis of the recurrent laryngeal nerve); the esophageal phenomenon, and the tracheobronchial phenomenon. The esophageal phenomenon is shown best

on an oblique view when a thick barium meal is used. There is a decided slowing of passage of the barium, a widening of the esophageal shadow, indentations of the shadow in the auricular region and pulsations transmitted to the barium mixture. The tracheobronchial phenomenon is a widening of the angle of the main bronchi at the hilus to over 77 degrees and a lifting and arching of the left main bronchus, demonstrated by a small instillation of iodized oil. On the oblique view of the left side the auricle salient as well as an irregular narrowing of esophageal shadows is present. The shadows in the pulmonary field are too well known to require comment.

In a study of brain metastases in cancers of the lung, Hernandez and Irogoyen found that 8 per cent of 50 patients had such metastases, which were recognized clinically, and that pulmonary symptoms always preceded cerebral symptoms.

Aguilar and Sirlin studied the so-called round infiltrates (Wartenhorst-Albert foci). The authors correctly state that the designation is ill advised. There are many varieties of pathologic conditions, from thinly encapsulated to heavily encapsulated caseous infiltrations. Some are calcified, some become resorbed and some excavate. They may be part of a primary infection, the "precocious type of Redeker" or "evolutive budding" type. The role of the bronchi, constitution, immunity and reaction of local tissue are discussed. The differential diagnosis is thoroughly given. It is concluded that although "round infiltrates" are generally quiescent foci they may be reactivated to disease. In spite of the similar appearance in the roentgenogram, they are not an "independent nosologic process."

Meccheri thoroughly studied venous pressure in normal and many pathologic conditions. The cause of high pressures is primarily cardiac insufficiency or local interference with circulation. Serial readings have some prognostic value in determination of trends in cardiac function. They may be used to differentiate edemas, cyanosis, enlargement of the liver and other conditions of noncardiac origin.

Other reports are of less practical value, but nearly all reflect a high order of work.

Medical Education and the Changing Order: Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. By Raymond B. Allen, M.D., Ph.D. Price, $1.50. Pp. 142. New York: The Commonwealth Fund, 1946.

In this readable little volume Dr. Allen, president-elect of the University of Washington, presents his views of what should constitute a medical education. The discussion is from the point of view of his extensive experience as dean of the schools of medicine, pharmacy and dentistry of the University of Illinois.

The first need in medical education is to bring together good teachers and good students. The environment ought to be conducive to developments which reflect not alone the scientific but also the cultural, social and economic aspects of society. With the community losing its complacency about poverty, industrial unrest and social deficiencies generally, more is demanded of the physician and of the medical education which must prepare him for this broader field. Physicians always will be occupied in replacing the damage caused by disease and maladjustments, but preventive medicine will occupy a larger part of his attention in the future, which means that he must be a broadly informed and cultured person to command the respect of leaders in the many phases of human activity of the changing order. The medical profession otherwise is likely to degenerate to the level of a trade.

Medical education, Dr. Allen believes, shares in the responsibility for the failure of the medical profession to exhibit social insight and exert sufficiently aggressive leadership in developing procedure for better distribution of the expanding technology of medicine. The gap in medicine between the "know how" and the "doing" for the benefit of all the people can be closed only by physicians who have social as well as technical training. Medicine has been concerned so long, so intensively and so successfully with ill health and disease that it has occupied itself too little

with the subject of good health. Medical education should stimulate the building of this superstructure to meet fully the needs of the times in regard to health.

Of graduate medical education, Dr. Allen implies that provision of experience in research is essential for a truly graduate university discipline. Programs falling short in this requirement are merely training for proficiency, and, important though this training is, no one ought to be misled into regarding the clinical specialist as a scientist. The library, the various conferences and the seminars all serve educational objectives. A well run graduate program provides these facilities in abundance. Standards of licensure and certification are important, but medical education ought to be concerned primarily with the development of the highest possible standards of learning and performance of which the student, intern, graduate student or practicing physician is capable.

The recruiting of good candidates for a medical education is a responsibility which physicians ought to take more seriously. Physicians know more about the family background and aptitudes of the young persons of their acquaintance than is possible perhaps for any one else to know; yet few physicians do much about encouraging gifted youths to study medicine. Medicine needs both scientifically and socially minded people, and the prospective student should be one who has tolerance, kindness, friendliness, dependability, industry, integrity, honesty, courage and determination. There is no room for any other kind, because medical schools are interested in producing only good physicians.

A physician should be sensitive to the values of beauty, goodness and wisdom as these values are conveyed by the creative arts and religion. And if medicine is to progress as a social as well as a biologic science, it must broaden its outlook and adjust its educational program. To bring premedical and medical curriculums up to date, one must recognize the fact that medicine has outgrown the limitations of the laboratory and the clinic. Pertinent phases of the disciplines of the social sciences and humanities should be among required studies.

These and the many other challenging conclusions of the author make this book worth reading by all intelligent persons, be they laymen or physicians. For those involved in medical education the book should be required reading.

The Duodenal Glands of Brunner in Man, Their Distribution and Quantity: An Anatomical Study. By Erik Landboe-Christensen. Price, 20 kroner. Copenhagen: Ejnar Munksgaard, 1944. London: Humphrey Milford, Oxford University Press, 1946.

This is a detailed anatomic investigation of the location, arrangement and quantity of the duodenal glands of Brunner in man, based on the observations in 53 cadavers of all age classes examined by a gross staining technic. By direct observation of the stained duodenums in surface view and, after they were embedded in gelatin, in profile section, the author has elucidated the topography of the glands and has estimated the quantitative glandular density throughout the area. Histologic details other than the form of the glands and glandular islands have not been considered. Extensive descriptions accompanied with maps showing the extent of the area of the Brunner glands and the density of glandular distribution are given for each individual specimen.

The author has found that proximally the area of the Brunner glands borders along the pyloric ring, on which it gradually encroaches and frequently crosses with advancing age. The distal delimitation was shown to be less definite: in five sixths of the cases isolated islands of glandular tissue were discovered to extend to a point midway between the inferior duodenal papilla and the commencement of the jejunum. In nearly two thirds of the cases Brunner glands were found to extend down as far as 4.5 cm. into the jejunum. In 6 of the 53 cases the most distal glands were present at the level of the inferior duodenal papilla. The density of the glandular tissue was found to be subject to a high degree of variation between individual specimens; in general, the acinar substance is densest proximally and gradually decreases to isolated glandular islands distally. The relative density was shown to be greatest in youth and the absolute density greatest in

middle age There is a gradual reduction of the total glandular substance with advancing years. The author observed that the density is usually least on the wall facing the pancreas.

The frequency of pathologic changes in adjacent structures being considered, surprisingly little attention has been paid to the duodenum by physiologists and anatomists until recently, slight importance being attached to this viscus in relation to allied clinical pathologic conditions. Currently, however, the organ is being studied more and more, and a comprehensive investigation of one of the major components of the duodenum, such as is here presented, is therefore timely.

Medical Clinics of North America. Boston Number: Symposium on Specific Methods of Treatment. Pp. 244. Philadelphia: W. B. Saunders Company, 1946.

This symposium on therapy brings the internist and general practitioner up to date on a variety of interesting and timely subjects. The field is not limited to purely medical problems alone, for it includes discussions on general surgery, otolaryngology, gynecology and urology from the medical viewpoint. Of particular interest is the article entitled "Medical Aspects of Renal Insufficiency in Urologic Practice" After the pathologic physiology of urinary obstruction, urinary infection and certain functional abnormalities of renal blood flow are discussed, the diagnostic procedures and therapy are presented, outstanding both in clarity and in physiologic approach.

Several of the purely medical articles offer nothing more than a brief review of well known and clinically proved diagnostic and therapeutic measures. Special mention should be made, however, of the thorough and enlightening presentations of the viral diseases, the anemias and diabetic coma. A clinical appraisal of streptomycin, Demerol (1-methyl-4-phenyl piperidine 4-carbonic acid), Benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride) and Pyribenzamine (N'pyridil-N'benzyl-N-dimethylethylenediamine) is submitted. Psychosomatic medicine is given a place in the consideration of obesity and neurocirculatory asthenia. Finally, an extremely stimulating clinicopathologic conference on amyloid kidney brings this uncommonly recognized disease to mind.

As a whole, the articles are well chosen and well presented, but the reviewer would like to have seen discussions of the more recent advances in hyperthyroid and diabetic therapy.

Om strumaproblemet paa grundlag af en undersøgelse i tre danske landsogne (The Goiter Problem Elucidated Through Studies in Three Rural Districts in Denmark). By Knud Rosenquist. Pp. 389. Copenhagen: Ejnar Munksgaard, 1943.

This rather lengthy monograph deals with an extremely careful, thorough and intelligent investigation of the incidence of endemic goiter among the rural population of Denmark. As studies elsewhere have also shown, areas with a high incidence of goiter were found to have little iodine in the drinking water. The finding of similarly low iodine content in the drinking water of districts without particularly high incidence of goiter suggests the existence of other factors in the production of goiter than lack of iodine alone. The monograph is in Danish, but there is an excellent English summary by Dr. Hans Andersen.

Syndrome cortico-pleural: son étude clinique et experimentale. By J. Skladal. Price, 160 fr. Pp. 144. Paris: Masson & Cie, 1946.

Skladal presents some of the more important clinical manifestations of the "corticopleural" syndrome which follows chronic pleural inflammation with fibrosis. The clinical discussions are supplemented by theoretic and experimental considerations. Many good roentgenograms are presented. This is an interesting monograph which should be of value to internists, phthisiologists and physiologists.